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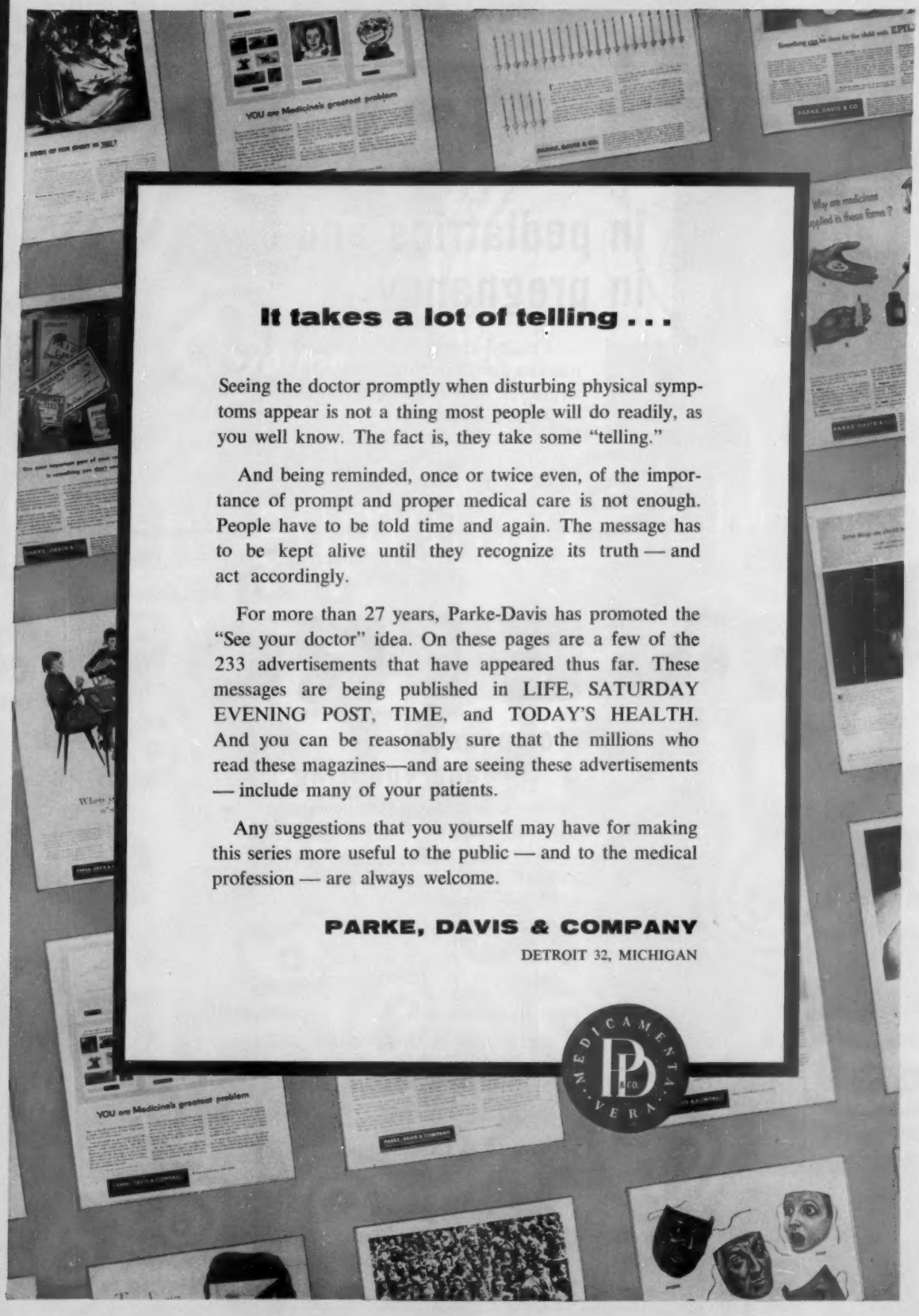

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1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.

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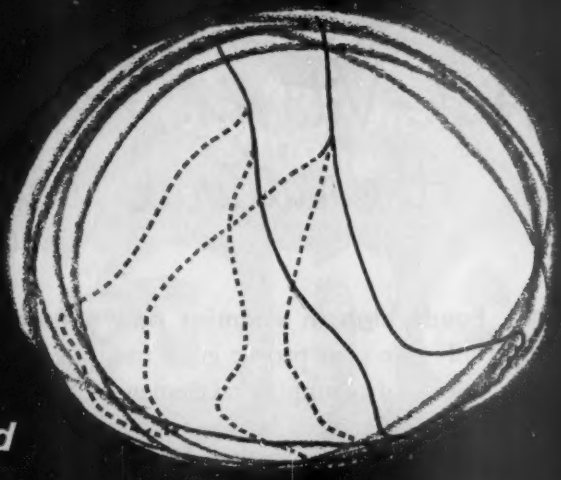

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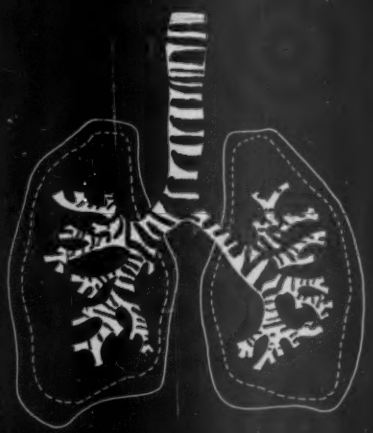

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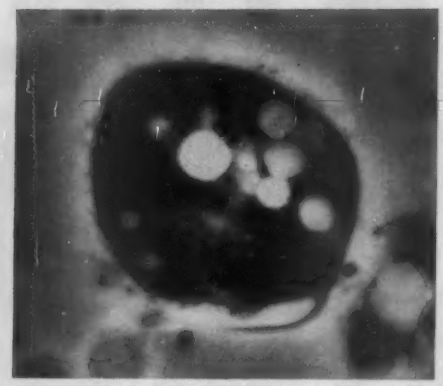

Phase-contrast microscope shows a trichomonad in a mucinous vaginal smear.

MANY trichomonacides failed in years past largely because they reached only the parasites swimming freely in the vaginal canal—not those hiding under epithelial cells deep among the vaginal rugae. In fact, some agents actually coagulated the albuminous material lining the surface and protected the trichomonads![1]

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The Davis technic.† Dr. Davis recommends a combination of office treatments and home treatments, using both VAGISEC jelly and liquid in home treatments. "A few women have infected cervical, vestibular or urethral glands and require other types of treatment. . . ."[2] It is well to remember the role of the male as carrier of the organism and prescribe protection against re-infection from the husband.[2]

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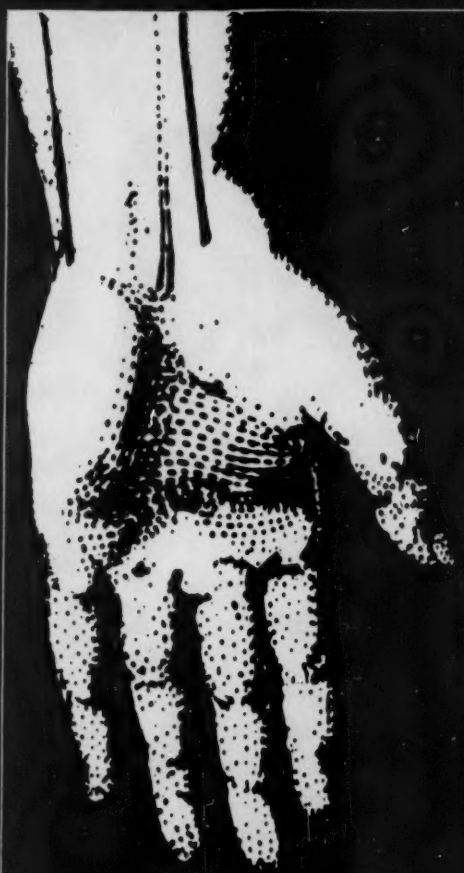
1. Davis, C. H.: Am. Jour. Obst. & Gynec. 68:559 (Aug.) 1954.
2. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955.
3. Davis, C. H.: J.A.M.A. 157:126 (Jan. 8) 1955.



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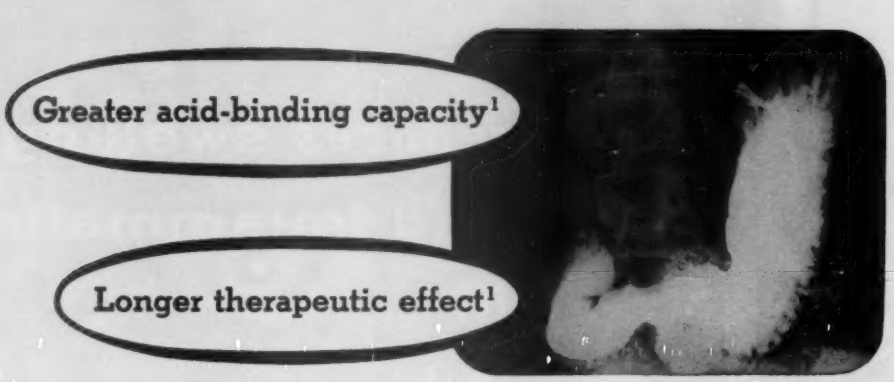

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1. Rossett, N.E., Rice, M.L. Jr.: An In Vitro Evaluation of the More Frequently Used Antacids, Gastroenterology 26:490 (1954).
2. Morrison, Samuel: Magnesium Aluminum Hydroxide Gel in the Antacid Therapy of Peptic Ulcer, Am. J. Gastroenterology 22:309 (1954).

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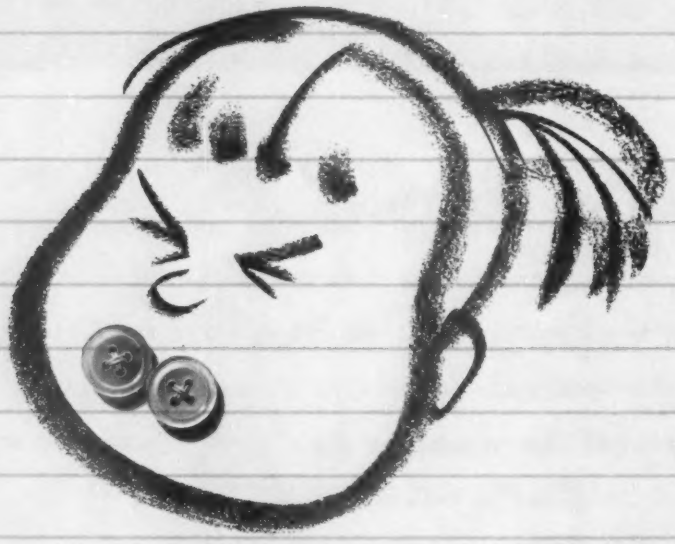

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1. Welch, H.: Personal communication

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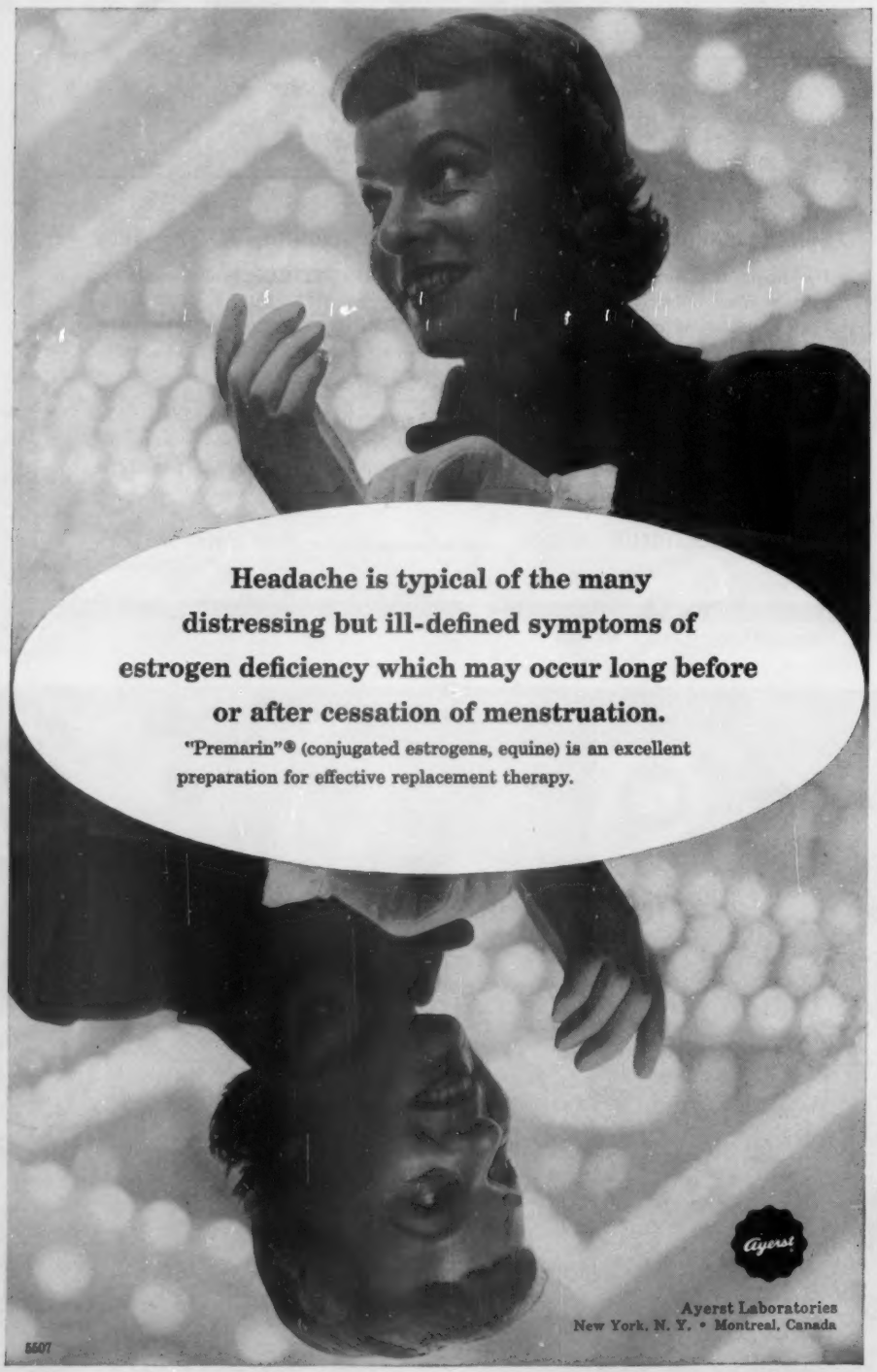
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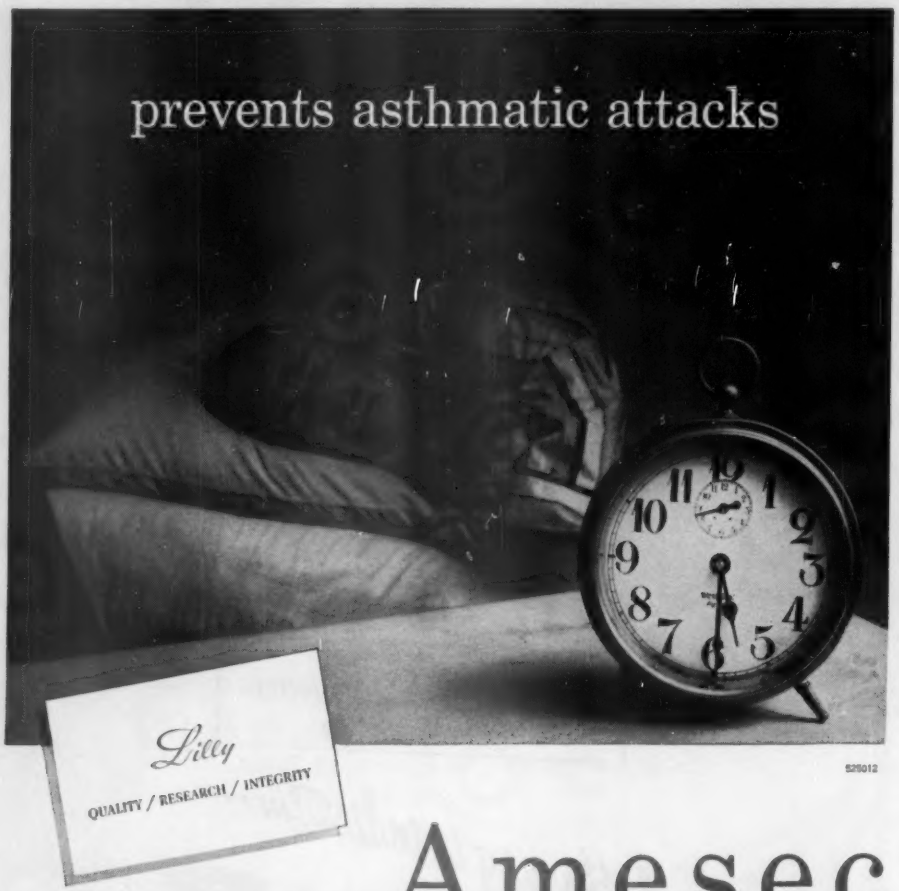

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Volume 253 NOVEMBER 10, 1955 Number 19

MULTIPLE POLYPOSIS OF THE COLON, OSTEOMATOSIS AND SOFT-TISSUE TUMORS

Report of a Familial Syndrome*

PROVIDENCE, RHODE ISLAND, AND BOSTON, MASSACHUSETTS

ROBERT S. WEINER, M.D.,† AND PHILIP COOPER, M.D.‡

ON the Surgical Service of the Veterans Administration Hospital, Providence, Rhode Island, we have had the opportunity to observe and treat 3 brothers with an unusual combination of abnormalities.

In reviewing the literature we have found a similar syndrome described in only 1 other family. It was believed that the case histories of these brothers should be studied and reported in view of the rarity of this disease syndrome.

Gardner et al.[1-3] reported multiple cutaneous and subcutaneous lesions occurring simultaneously with multiple polyposis of the colon and osteomas in 6 members of a family group of 51 living persons. Forty-four members of the family group were free of all three abnormalities, and 1 member, a child, had only subcutaneous tumors. The bone tumors occurred primarily in the mandible and maxilla, but were also found in other parts of the skeleton.

There were three types of cutaneous or subcutaneous tumors–epidermoid cysts, fibromas and poorly defined masses of connective tissue. There was widespread distribution of the lesions, which occurred on the head, back, chest and abdomen and extremities. They were always multiple, and as many as 26 were found on 1 patient.

Eight family members, then deceased, were reported to have died of cancer of the colon and rectum. The diagnosis was confirmed by microscopical examination in 2 cases. Six persons were reported to have had osteomas, and all 8 were known to have had subcutaneous tumors or cysts.

Gardner and his associates[1-3] concluded that a single defective gene with a dominant mode of inheritance was the most likely explanation for the presence of all three abnormalities in the family group studied.

Recently, we encountered a family group that we believe presents the same syndrome described by Gardner et al.[1-3] Three brothers were studied in the Veterans Administration Hospital in Providence, and another at a neighboring hospital. The 3 brothers were found to have multiple polyposis of the colon, osteomatosis and multiple soft-tissue tumors. All 3 patients have been subjected to ileostomy and total colectomy. The resected bowel specimens revealed adenocarcinoma of the rectum or colon, or both, in 2, in addition to the multiple polyposis. The fourth brother, who was hospitalized and studied elsewhere, had an ileostomy and total colectomy performed for multiple adenocarcinomas of the large bowel. X-ray examination of the skull showed multiple exostoses. No soft-tissue tumors were found.

We have encountered considerable difficulty studying the rest of the family because of their lack of cooperation. The mother of the patients died in her early thirties, after an operation for gall-bladder disease. The father was admitted to another hospital in June, 1954, when a vagotomy was performed for peptic ulcer. He had no clinical evidence of any of the three abnormalities.

The patients had 3 sisters, all of whom were advised of the need for a thorough examination. Thus far, only 1 has had a physical examination and barium-enema study, no evidence of the abnormalities being uncovered.

The 4 brothers and 3 sisters have had 10 children to date. Thus far, none of the children have been examined despite the fact that their respective parents have been advised of the necessity for periodic check-ups.

CASE REPORTS

CASE 1. A.D., a 36-year-old married male tool grinder, entered the Veterans Administration Hospital in Providence

*From the Surgical Service, Veterans Administration Hospital, Providence, Rhode Island, and the Department of Surgery, Boston University School of Medicine.

†Assistant in surgery, Boston University School of Medicine; resident in surgery, Veterans Administration Hospital.

‡Associate professor of clinical surgery, Boston University School of Medicine; chief, Surgical Service, Veterans Administration Hospital.

for the 2d time on January 1, 1954, with a chief complaint of a mass of 3 months' duration in an epigastric scar.

In 1934, at the age of 16, he had six operations at another hospital for the removal of tumors of the mandible, of the temporomandibular joints, from the back of the right ear and over the 3d right rib. The findings were reported by Thoma.[4]

In 1944 rectal bleeding developed while he was in the Army. He was told that he had polyps in his colon. In

FIGURE 1. *Roentgenogram in Case 1, Demonstrating Exostoses of Skull, Sinuses and Mandible.*

April, 1947, he had a hemorrhoidectomy at another hospital for rectal bleeding.

He was hospitalized initially at the Providence Veterans Administration Hospital on February 26, 1952. At that time he gave a history of having had rare attacks of mild rectal bleeding for 3 years, and frequent attacks of diarrhea of 8 months' duration. Physical examination revealed a well developed, well nourished man in no acute distress. The scars of the previous operations for the removal of osteomas were noted. Abdominal examination was negative. On rectal examination a slightly firm mass was felt just within reach of the examining finger. Sigmoidoscopy showed a generally reddened friable mucosa and a 4-cm., firm, friable mass protruding into the rectal lumen at about 13 cm. A biopsy was reported as indicating adenocarcinoma of the rectum. Laboratory examination revealed a hemoglobin of 12 gm. per 100 cc. and a white-cell count of 6700, with a normal differential. Urinalysis was negative, as was a blood Hinton test. X-ray examination of the chest was also negative. Barium-enema study showed multiple polyposis of the colon and possible narrowing of the rectosigmoid. An upper gastrointestinal x-ray series was negative. A skeletal survey revealed multiple exostoses of the skull, sinuses, mandible, humerus, radius, metacarpals, tibia and fibula (Fig. 1-4). On March 13, an abdominoperineal resection of the rectum and sigmoid was performed. Examination of the operative specimen disclosed an adenocarcinoma of the rectum, an adenocarcinoma of the sigmoid, with metastases to regional lymph nodes, and multiple polyposis of the rectum and sigmoid, with malignant degeneration of adenomatous polyps. On April 16 the colectomy was completed, and an ileostomy was performed. Examination of that operative specimen revealed multiple polyposis of the terminal ileum, appendix and colon, and adenocarcinoma involving some of the adenomatous polyps (Fig. 5 and 6). The patient was discharged on May 1, 1952.

At the 2d admission he reported intermittent drainage from the perineal wound, and there was a lump in the incision through which the colectomy had been accomplished. There was a nontender, hard immobile mass, 6 cm. in diameter, deep in the abdominal wall under the transverse epigastric scar. A functioning ileostomy was present. There were several shallow sinus tracts in the perineal wound. Laboratory examination revealed a hemoglobin of 15.9 gm. per 100 cc. and a white-cell count of 6800. Urinalysis and x-ray study of the chest were negative. On January 12, 1954, the mass was excised. Exploration along the peritoneal surface of the scar in the region of the left rectus muscle disclosed numerous nodules, 2 or 3 cm. in diameter, under the peritoneum. Examination of the specimen revealed a fibroma. A photomicrograph of the lesion is shown in Figure 7.

This is the only patient in whom all three diagnoses, polyposis of the colon, osteomas and connective-tissue tumors, were proved pathologically. The fibroma arose at the site of an operative scar. It seems likely that the hereditary tendency to fibroma formation remained latent until trauma, in the form of an operative incision, made this tendency become overt in the form of a fibroma.

FIGURE 2. *Roentgenogram in Case 1, Showing Exostoses of Metacarpals and Phalanges.*

CASE 2. L.D., a 31-year-old married spark tester, entered the Providence Veterans Administration Hospital for the 4th time on July 19, 1954, with a chief complaint of pain in the abdomen, lower chest and left shoulder of 6 hours' duration.

The patient was first admitted to this hospital on March 10, 1953, with the chief complaint of hemorrhoids of 7

years' duration. There was no history of melena or diarrhea. Physical examination revealed a well developed, well nourished man in no acute distress. The abdomen was soft, with no palpable masses. Rectal examination showed internal and external hemorrhoids, and a polypoid mass palpable at the tip of the examining finger. The red-cell count was 3,490,000, with a hemoglobin of 10.1 gm. per 100 cc. and a hematocrit of 34 per cent and the white-cell count 9650, with a normal differential. A blood Hinton test was negative, and urinalysis was within normal limits. X-ray study of the chest disclosed no disease. Barium-enema examination revealed multiple polyposis of the colon. An upper gastrointestinal x-ray series was normal, as were films of the skull, pelvis, left femur, tibia and fibula, right radius and ulna. Sigmoidoscopy demonstrated multiple polyposis of the rectosigmoid. Biopsy of one of the rectal polyps showed it to be an adenomatous polyp with atypical hyperplasia. On March 27 ileostomy and subtotal colectomy were performed. The pathological report on the resected

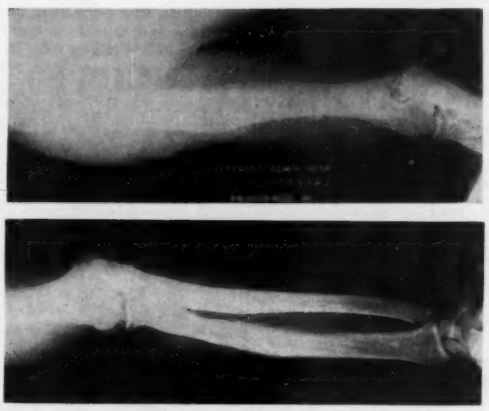

FIGURE 3. *Roentgenogram in Case 1, Showing Exostoses of Humerus and Radius.*

specimen was multiple adenomatous polyps of the colon. The patient was discharged on May 1.

He was readmitted to the hospital 10 days later and a combined abdominoperineal resection of the rectum and sigmoid was performed on May 18. The pathological diagnosis was adenocarcinoma of the sigmoid, with multiple polyposis of the rectum and sigmoid. The patient was discharged on June 5.

He was rehospitalized between November 25 and Novem-

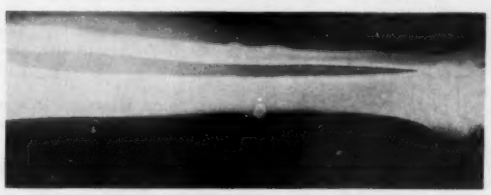

FIGURE 4. *Roentgenogram in Case 4, Demonstrating Exostoses of Tibia and Fibula.*

ber 27 with transient intestinal obstruction due to a tight ileostomy.

On the 4th admission, the patient was found to have a perforated gastric ulcer, which was sutured at an emergency operation on July 20, 1954. At the time of operation a firm mass, 6 cm. in diameter, was palpated in the lower end of 1 of the healed abdominal incisions. The mass did not extend intraperitoneally, and was thought to resemble a fibrous-tissue tumor. The postoperative course, which was stormy, was complicated by a staphylococcal enteritis, a probable pulmonary embolism and a transient internal gastrojejunal fistula. When he was sufficiently recovered he was examined carefully to determine the presence of any bony or other soft-tissue tumors. There was a slightly raised, 1-cm.-long, bony projection in the right frontal region, 2 1-cm.-long bony projections in the left frontal region, a soft, movable subcutaneous lesion, 2 cm. in diameter, along the

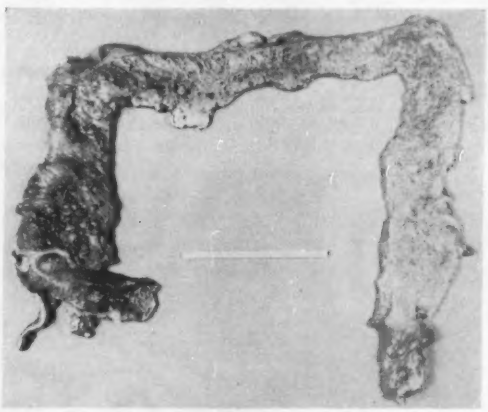

FIGURE 5. *Specimen of the Colon, Appendix and Terminal Ileum in Case 1, Showing Polyposis, with Adenocarcinoma Involving Some of the Adenomatous Polyps.*

posterior border of the right sternocleidomastoid and a soft, movable tumor, 1 cm. in diameter, over the lateral aspect of the left elbow. He was discharged on September 22.

He was readmitted to the hospital 1 week later. Gastroscopy gave no evidence of polyps, tumor, gastritis or ulcer.

FIGURE 6. *Resected Specimen of the Rectum and Lower Sigmoid in Case 1, Showing Polyposis with Malignant Degeneration.*

The gastric antrum was well visualized. The patient was discharged on an ulcer regimen.

In this case the diagnosis of multiple polyposis was proved pathologically. A tumor that had all the gross characteristics of a fibrous-tissue tumor developed in an operative incision. This patient again illustrates

a latent tendency to form fibrous-tissue tumors. He had x-ray findings of osteomas of the skull. If it had been suspected that he had a carcinoma of the sigmoid, the abdominoperineal resection would have been accomplished before the subtotal colectomy.

CASE 3. M.D., a 34-year-old married rubber-shoe dipper, entered the Surgical Service of the Providence Veterans Administration Hospital for the 3d time on September 21, 1954, for the operative treatment of multiple polyposis of the colon.

In 1938 a mass in the right groin had been incompletely removed. The mass had been present as far back as he could remember. Surgical removal was attempted again in 1948 but was abandoned because the tumor involved the iliac and femoral vessels. A biopsy was obtained, however, and examination showed the tumor to be a desmoid.

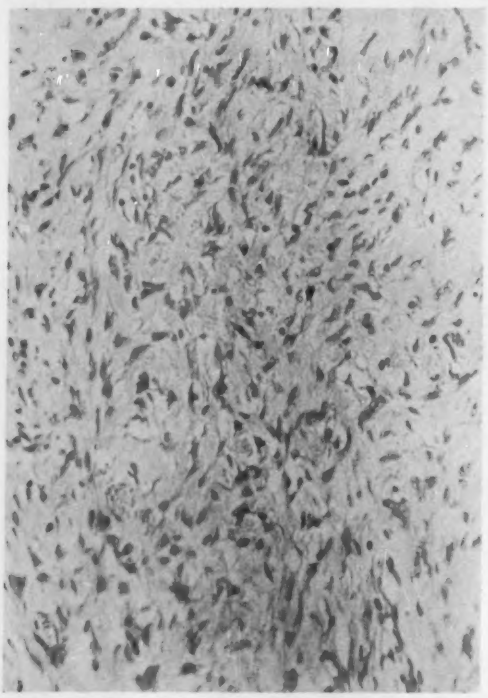

FIGURE 7. *Microscopical Field of Fibroma Excised from the Abdominal Wall in Case 1.*

The patient was admitted to the Providence Veterans Administration Hospital for the 1st time on August 8, 1952, complaining of epigastric pain occurring between meals and relieved by food and antacids. Physical examination revealed the mass in the right groin and the absence of the right testicle. An upper gastrointestinal x-ray series disclosed an active duodenal ulcer. The ulcer responded well to a medical regimen, and he was discharged on August 15, 1952.

He was admitted to the hospital for the 2d time on July 8, 1954, with the chief complaint of diarrhea for 3 days that had also occurred 2 weeks previously. Physical examination revealed a well developed, well nourished man. There was a small, firm, bony projection over the left maxilla, several small subcutaneous tumors over the chest and a small, soft tumor over the left midportion of the abdomen. The presence of the large, firm mass in the right groin and the absence of the right testicle were again noted. An exostosis on the medial aspect of the right humerus was also observed. On rectal examination, 6 to 8 soft, nonfriable polyps were found. Sigmoidoscopy revealed diffuse polyposis of the rectosigmoid. The hemoglobin was 14.2 gm. per 100 cc., and the white-cell count 7800, with a normal differential. The blood Hinton test was negative, and urinalysis was within normal limits. Barium-enema study showed that the entire colon contained many polyps. A gastrointestinal x-ray series revealed a healed duodenal ulcer. On x-ray examination of the skull multiple small exostoses of the skull, multiple osteomas of the ethmoid sinuses and a complex composite odontoma in the posterior ramus of the right mandible were found. A total colectomy was recommended at that admission, but the patient requested postponement to take care of personal affairs. He was discharged on July 27.

He was admitted to the hospital for the 3d time on September 21. On October 4 a 1-stage ileostomy and total colectomy was performed. In addition an intra-abdominal right testis was removed, and a biopsy of the desmoid tumor was obtained. Examination of the resected specimen of bowel revealed multiple polyposis, with no evidence of malignant change. The biopsy of the edge of the tumor of the groin revealed acellular collagen and some adipose tissue. Convalescence was complicated by transient intestinal obstruction and by probable thrombophlebitis. The patient was discharged on November 8, with the ileostomy functioning properly and with the perineal wound almost healed.

This patient had multiple polyposis of the colon, with a fibrous-tissue tumor demonstrated pathologically and exostoses demonstrated radiographically. He had multiple soft-tissue tumors, some of which had the physical characteristics of fibrous-tissue tumors or cysts.

A duodenal ulcer was demonstrated by x-ray examination. This was the only 1 of the 4 brothers studied in whom carcinoma of the colon was not found at operation.

The life history of this patient's fibrous-tissue tumor merits further study, since very cellular tumors were apparent on the first two biopsies and primarily mature collagen on the last. It is possible that biopsy in a different area would have shown noncellularity, indicating that the period of rapid growth of the tumor has ceased.

CASE 4.* J.D., a 28-year-old married textile inspector, entered another hospital for the 1st time on February 25, 1953, with the chief complaint of diarrhea and abdominal pain of 3 months' duration. Physical examination revealed a thin, pale man in no acute distress. Abdominal examination was negative. On rectal examination a large, firm, indurated, annular growth was felt 5 cm. from the anus. Examination of the blood disclosed a hemoglobin of 87 per cent (Sahli) and a white-cell count of 9100, with a normal differential. Urinalysis and a blood Hinton test were negative. Sigmoidoscopy revealed a large polypoid mass 5 cm. from the anus, with several smaller polyps visible at a higher level. A biopsy was taken, and microscopical examination showed an adenomatous polyp. On barium-enema examination numerous polyps of the rectum, sigmoid and descending colon were observed. Barium was stopped at the mid-descending colon by an obstruction. The x-ray diagnosis was polyposis of the colon, with a napkin-ring carcinoma of the mid-descending colon. X-ray study of the chest was negative. Films of the skull revealed numerous exostoses and enostoses of the skull and mandible. On March 3 a subtotal colectomy and ileostomy was performed, the colon from cecum to lower sigmoid being removed in the process. Gross examination of the operative specimen revealed 2 large, cauliflowerlike, pedunculated polyps and 25 smaller ones at the ileocecal valve and in the cecum, and roughly 200 polyps, 0.8 to 2.5 cm. in

*Reported with the permission of Cornelius H. Hawes, M.D., of the Truesdale Hospital, Fall River, Massachusetts.

diameter, scattered throughout the rest of the colon; 8 cm. proximal to the distal end of the resected specimen there was a cauliflowerlike projection, 3.5 cm. in diameter, with an ulcer at its apex. The serosa was invaded. Microscopical examination indicated an adenocarcinoma of the sigmoid, with lymphatic invasion, papillary adenocarcinoma of the cecum, benign polyps of the colon and adenocarcinoma metastatic to the mesenteric lymph nodes. The patient was discharged home on March 19, 1953, to return in about 2 weeks for combined abdominoperineal resection of the rectum and rectosigmoid.

He was admitted to the same hospital for the 2d time on March 28, complaining of vomiting and weakness of a few hours' duration. He had become depressed while at home and had very little oral intake since discharge from the hospital. After hydration, correction of electrolyte imbalance, adjustment of diet and psychotherapy, his general condition and attitude improved, and he was discharged on April 28, to return in a few weeks for the final stage of his operation.

On September 3 a combined abdominoperineal resection of the rectum and rectosigmoid was carried out. At operation an extensive tumor of the rectosigmoid was found. The tumor could not be totally removed. Gross examination of the specimen revealed a 7-cm., ulcerated, cauliflowerlike lesion 4 cm. proximal to the anus. Microscopically, the tumor extended through the mucosa. The microscopical diagnosis was carcinoma of the colon, with lymphatic invasion, and carcinoma of the rectum and sigmoid. The patient was discharged on September 17.

He was readmitted to the same hospital for the 4th time on June 15, 1954. He had had bleeding from an obvious recurrence of carcinoma in the perineal wound. Physical examination revealed a pale, emaciated man. On abdominal examination a large mass was palpated in the left lower quadrant, firm, enlarged lymph nodes in both groins, and an ulcerating lesion 5 by 3 cm., in the perineal incision. He was discharged on June 18 and died at home several months later. No autopsy was performed.

This patient had multiple polyposis of the colon proved pathologically. In addition he had osteomas proved radiographically. There was no evidence of soft-tissue tumors on physical examination. It is possible that a probable latent tendency to fibrous-tissue tumor formation did not become evident because of his early death.

If it had been suspected that this patient had carcinoma of the rectum, as well as of the colon, a one-stage procedure would have been performed.

Discussion

The familial syndrome of multiple polyposis of the colon, osteomatosis and soft-tissue tumors is apparently rare in view of the fact that only 1 report of such a syndrome has been found in the literature.

Carcinoma of the colon is just as likely to develop in patients with this syndrome as in those with the more common variety of multiple polyposis of the colon.

X-ray examination of the bones of all members of any family in which this syndrome appears may help determine in which members polyposis will develop, for it is possible that the bony changes may be the first manifestation of this disease, as in Case 1.

It should also be realized that fibrous-tissue tumors may develop in any incisions in these patients.

Summary

Case reports of 3 brothers with a unique syndrome of multiple polyposis of the colon, osteomatosis and soft-tissue tumors are presented. A fourth brother had multiple polyposis of the colon and osteomas.

It is believed that this is the second family in which this syndrome has been reported.

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CLINICAL VALUE OF A TRACING OF FORCED EXPIRATION (EXPIROGRAM)*

I. Pulmonary Disease

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Francis C. Lowell, M.D.,§ and Irving W. Schiller, M.D.¶

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THE accessibility of the lungs to physical and roentgenologic examination has enabled clinicians to diagnose and manage a great many pulmonary diseases without resort to measurements of pulmonary function. There are many cases, however, in which physical examination and x-ray studies do not give enough information for proper management.

Tests have been developed that are at least as informative about the various functions of the lungs as those widely used in cardiac, liver and renal disease. Nevertheless, pulmonary function is rarely assessed as part of routine clinical management unless an interested group and a specially equipped laboratory are readily available. Such studies generally include a variety of tests requiring relatively

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elaborate equipment, highly trained personnel and considerable effort and co-operation on the part of the patient. Although these tests are valuable in diagnosis, management and prognosis and are widely used to assess the hazards of surgery, less cumbersome procedures are required if the evaluation of lung function is to be feasible for most clinicians.

The only widely used test of pulmonary function to date is the vital capacity. This is of very limited usefulness even though a significant decrease is encountered in many common conditions, including

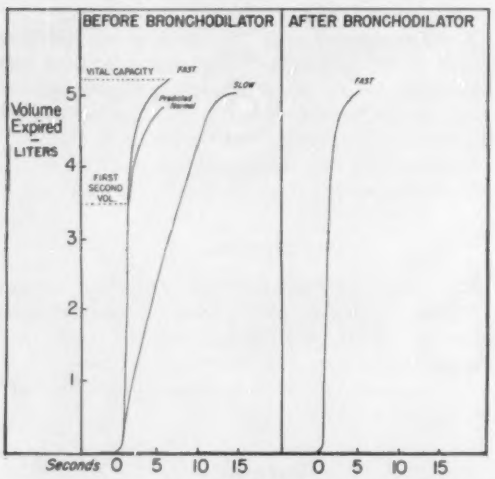


FIGURE 1. *Normal Expirogram, before and after Bronchodilatation, of A.M., a Thirty-One-Year-Old Man, 188 Cm. (6 Feet, 2 Inches) Tall, on January 1, 1955.*

restrictive disease of the lung, cardiac failure, bronchial asthma and pulmonary emphysema. Occasionally, in bronchial asthma and frequently in emphysema, the decrease, when present, is far less than would be anticipated from the degree of functional impairment.

When bronchial obstruction is present, measurements that take into account the expiratory rate in addition to the total amount expired are much better indications of functional impairment, and this may be true in other conditions that do not appear to be primarily obstructive.[1] It is for this reason that the maximum breathing capacity, a test with a number of disadvantages, occupies such a prominent place in clinical pulmonary physiology.

Numerous workers have been concerned with the rate of airflow during a maximal forced expiration. Cournand et al.[2] noted a striking decrease in the rate of expiration in pulmonary emphysema. Motley[3] concluded that the volume expired in the first three seconds was a useful index of pulmonary disability whereas Gaensler[4] suggested that the volume expired in the first second was of great clinical value. Comroe and his associates[5] called attention to the changes in the configuration of tracings made during forced expiration by patients with various pulmonary disorders. The interest expressed by these workers and by others[6] is, in our opinion, well warranted. Our purpose here is to urge the application of these measurements on a much wider scale. For clinical purposes we believe that a kymographic tracing of maximal forced expiration is particularly valuable. In addition to the measurements mentioned above, a complete record of the events occurring throughout expiration is obtained. For brevity the tracing made in this manner is referred to as the "expirogram."

METHODS

The tracings were made with a spirometer of 6-liter capacity having a diameter of 16 cm. and recording on an adjustable-speed kymograph run at 0.56 cm. per second, a speed satisfactory for analysis of the events occurring during forced expiration.

We found a nose clip unnecessary as a rule. Patients were instructed to take as deep a breath as possible, to put their lips around a mouthpiece attached by large-caliber tubing to the spirometer and then to exhale forcibly and rapidly in the conventional manner. The greatest possible rate of expiration is often obtained with a degree of effort well below the maximum of which the patient is capable. Indeed, the paradox that a maximal effort yields a slightly slower rate of expiration than one that is submaximal is occasionally seen in patients with obstructive disease. It is generally not appreciated that satisfactory tracings are obtainable without the violent effort often demanded of patients doing procedures of this type. Whether the patient expires with maximal or submaximal force, the effort should be maintained until no further air is leaving the lungs. Again, if patients with obstructive disease deliberately expire at a rate less than their maximum, the volume expired may be greater than that obtainable at the maximum rate of expiration. This is a manifestation of "trapping,"[7,8] and here the tracing supplies evidence that expiration was indeed performed slowly. The maneuver was included in these studies, and curves so obtained are indicated in Figures 1 to 3 by "slow." Tracings were obtained before and after six inhalations of a bronchodilator aerosol.*

CHARACTERISTICS OF THE NORMAL EXPIROGRAM

The "normal" vital capacity can be estimated from the patient's age and height according to a widely used formula.[9] It should be remembered that such calculated values represent averages and that in practice a wide range is seen. A normal expirogram is shown in Figure 1. An adult subject who exhales rapidly in the usual manner expels in

*Isopropylarterenol, 1:200 solution, from a No. 40 DeVilbiss nebulizer.

the first second a volume of 70 to 85 per cent of the vital capacity. Children will expire more than 85 per cent in the first second, often completing expiration within one second. On the other hand, elderly persons, apparently well, may expire less rapidly than young adults. Hence, as little as 70 per cent may be expired in the first second by elderly subjects with no evidence of pulmonary disease. Unless a normal subject exhales forcibly, irregularities in the curve may be produced. A voluntary effort on the part of a person with normal lungs to imitate tracings produced by patients with pulmonary disease yields readily recognizable irregularities that are incompatible with an expiration done with force. Thus, malingering is easily detected.

In the absence of pulmonary disease we have observed no change in rate of expiration or vital capacity after the administration of a bronchodilator drug. However, with the kymograph speed used in these studies (0.56 cm. per second) the slope of the initial portion of the normal expirogram is so steep that one cannot be sure that a small change in rate does not occur. The speed selected is satisfactory for most patients with clinically significant degrees of pulmonary disease. Speeds greater than 1 cm. per second yield cumbersome records, especially in emphysema, and tracings made with speeds less than 0.5 cm. are difficult to interpret.

Bronchial Asthma

Experience with the expirogram in the past eight years has convinced us that it is the most useful objective means of evaluating the severity of asthma. Physical findings are often misleading because their intensity does not correlate well with the severity of the disease. A patient with mild asthma may have marked wheezing, whereas one with severe asthma may have little or no wheezing. Indeed, we have noted that in attacks artificially induced by the administration of an aerosol of histamine or allergen, wheezes may not become prominent until after the attack has passed its peak and has begun to subside. Although absent at rest, wheezing may become prominent if ventilation increases for any reason. Many patients are poor judges of the severity of the asthma that they have. One who has been having severe asthma may be quite content with partial relief even though the lungs are still extremely abnormal.

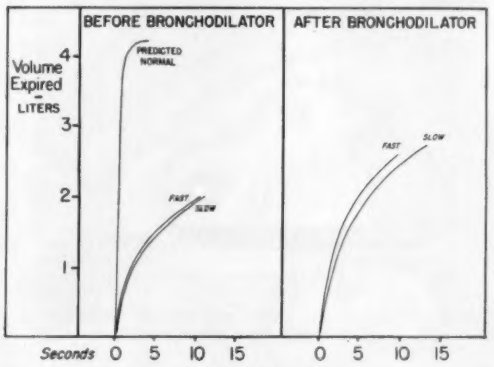


Figure 2. *Expirogram in Case 1.*
This patient, a sixteen-year-old boy with bronchial asthma, was 168 cm. (5 feet, 6 inches) tall.

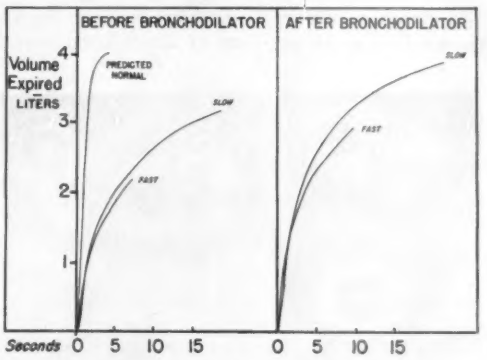


Figure 3. *Expirogram in Case 2.*
This patient, a fifty-one-year-old man with chronic obstructive emphysema, was 178 cm. (5 feet, 10 inches) tall.

The following case illustrates the characteristics and usefulness of the expirogram in bronchial asthma.

Case 1. P.J., a 16-year-old boy, was admitted to the hospital on December 18, 1954, because of severe asthma. He had had cough, shortness of breath and wheezing since early infancy. During puberty his symptoms lessened, but in November, 1953, he had a marked exacerbation and was admitted to another hospital. Since then he had never been free of symptoms despite treatment with bronchodilator drugs and cortisone given in a relatively small dosage for a short period. In November, 1954, he was again hospitalized elsewhere, but after discharge he continued to have difficulty and was admitted here. Although there was no striking seasonal incidence the asthma tended to be worse in the winter than in the summer. There had always been a dog at home, but the patient and his family were unaware of any relation between exposure to the animal and symptoms. The patient had had eczema in infancy, and a brother had asthma.

Physical examination showed a thin, well developed boy, 168 cm. (5 feet, 6 inches) tall and weighing 49.9 kg. (110 pounds), with respiratory distress and cyanosis of the skin and mucous membranes. The anteroposterior diameter of the chest was increased; the sternum was prominent, and the rib cage elevated. The neck and thoracic muscles were active in respiration; the percussion note was hyper-resonant, and both leaves of the diaphragm were low and fixed. There were numerous high-pitched inspiratory and expiratory wheezes. The rest of the physical examination was not remarkable.

The temperature was 98°F. by mouth, the pulse 110, and the respirations 30. The blood pressure was 118/84.

The urine was normal. The hemoglobin was 15.5 gm. per 100 cc., and the hematocrit 48 per cent; the white-cell count was 11,200, with 12 per cent eosinophils and an otherwise normal differential. An x-ray film of the chest taken on admission is shown in Figure 4. One taken 7 weeks later, when the patient was well, showed no change. Figure 5 demonstrates the more important features of the course,

and Figure 2 the effect of rate of expiration and bronchodilators on the expirogram.

The patient improved dramatically and on discharge stated that he felt better than at any time that he could remember. On the basis of the history and skin tests the dog was removed from the home, and the patient was treated with extracts of house dust and molds. He remained relatively well after discharge and was able to stop taking cortisone. He suffered a brief relapse approximately 2 months after discharge when a large dose of allergenic extract was followed by a constitutional reaction.

As shown in Figure 2, the vital capacity on December 19 was 48 per cent of a predicted normal

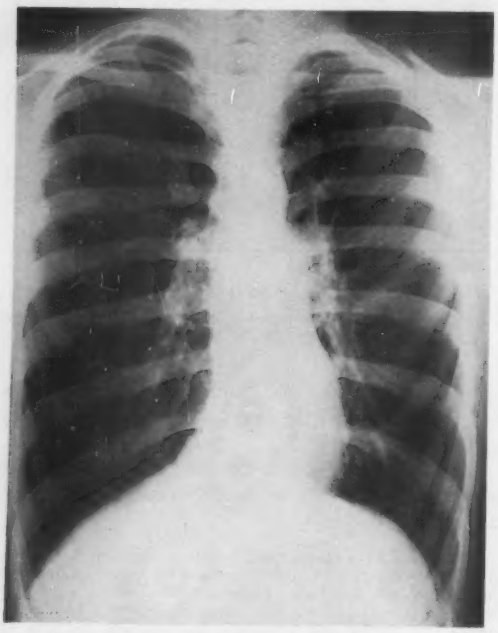


FIGURE 4. *Posteroanterior Film of the Chest on Admission in Case 1, Showing Radiolucent Lungs, Horizontal Ribs and Lowering of the Diaphragm.*

value of 4200 cc., but the expiratory rate was reduced even more. Before the administration of a bronchodilator, 650 cc. was expired in the first second, only 19.4 per cent of the predicted normal volume (3360 cc.) for this interval. Prompt changes in the expirogram could be induced with a bronchodilator, and all spirometric evidence of asthma disappeared after intense treatment with cortisone and bronchodilators (Fig. 5). As mentioned above, "slow" expiration may produce a greater volume than rapid expiration, but this was not seen in the case under discussion, nor is it so common in asthma as in emphysema.

The expirogram may improve after the administration of a bronchodilator, even in the absence of physical signs of asthma and at a time when the patient is unaware of any difficulty. This is evidence that some asthma is still present and that the therapeutic regimen should be continued or intensified. Such a situation is illustrated by Case 1. On December 22 (Fig. 5) the patient felt well, and there were no wheezes on auscultation although the expirogram was still abnormal. Improvement followed the administration of a bronchodilator, and therapy was consequently maintained at a relatively high level. It is our impression that patients are much less likely to relapse if they are maximally improved before medication is markedly reduced or stopped. This cannot be ascertained without some measure of pulmonary function, for which the vital capacity alone is not adequate. On the other hand, a relatively normal tracing indicates that a reduction in medication may be tolerated. This is especially important if the patient is receiving cortisone, when a minimal but effective dose is desirable.

PULMONARY EMPHYSEMA

There is disagreement concerning the fundamental disorder in chronic pulmonary emphysema. Some consider it primarily an abnormality of the parenchyma, which becomes easily stretched and ruptured, whereas others attribute these changes to inflammation of the bronchial tree, with consequent obstruction of the airway followed by secondary changes in the parenchyma. Regardless of the nature of the process, emphysematous patients exhibit obstruction to the outflow of air from the lungs, an increase in the residual volume,* a disturbance of intrapulmonary distribution of the inspired air and, in advanced cases, a decrease in oxygen saturation

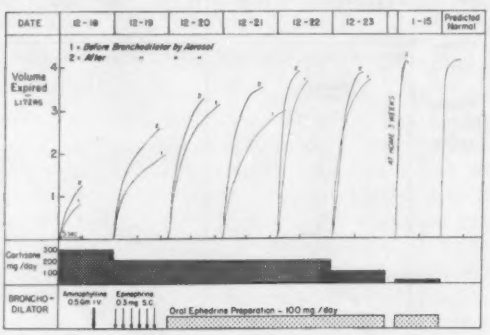


FIGURE 5. *Effect of Treatment on the Expirogram in Case 1.*

and an increase in arterial carbon dioxide. The need for an objective measure of pulmonary function as a guide to the patient's condition is even greater here than in asthma. Physical and roentgenologic findings are not sensitive enough to reveal the small changes in respiratory function that may make so much difference to the disabled patient. Although much can be learned from more elaborate procedures, the severity of the disease can be esti-

*The amount remaining in the lung at the end of a maximal expiration.

mated and its progress followed with the expirogram, as in the following case.

CASE 2. I.L., a 51-year-old married man, was admitted to the hospital on August 11, 1954, because of shortness of breath of 3 years' duration. Approximately 10 years previously he had had a transient episode of shortness of breath associated with a feeling of panic lasting 12 hours. Three years before admission he began to note shortness of breath not only on exertion but also when emotionally upset, and for 1 year he had a dry, nonproductive cough but no wheezing. He had smoked about ½ package of cigarettes daily for approximately 30 years. He was treated with physical therapy, injections of dust extract, cortisone and chiropractic manipulations. Except for a period of several weeks when he was receiving cortisone, he continued to be markedly dyspneic. About 3 weeks before admission shortness of breath became so severe that he could no longer carry on at work.

He had had a herniorrhaphy on the right 6 years previously and had urinary urgency and difficulty starting the stream for 6 months. His only son had hay fever and asthma.

Physical examination showed a well developed, tense, apprehensive man who was 178 cm. (5 feet, 10 inches) tall and weighed 78.5 kg. (173 pounds) and who had a dusky cyanotic hue to his face, lips and ears. He was breathing rapidly but was in no acute distress. The chest was slightly increased in anteroposterior diameter, and breathing was costal. The lungs were hyper-resonant, and both leaves of the diaphragm were low and fixed. A few low-pitched wheezes were heard anteriorly, and a few medium rales were heard over the right-posterior-lung fields. The abdomen revealed appendectomy and herniorrhaphy scars, and there was a left-sided inguinal hernia. The genitalia were not remarkable. Rectal examination revealed a moderately enlarged prostate. The extremities and neurologic examination were within normal limits.

The pulse was 88, and the respirations 19. The blood pressure was 124/70.

The urine was normal.

Examination of the blood showed a red-cell count of 5,600,000 with a hemoglobin of 15.8 gm. per 100 cc. and a hematocrit of 47 per cent; the white-cell count and differential were normal. The blood urea nitrogen was 17 mg., and the fasting blood sugar 72 mg. per 100 cc. The venous-blood carbon dioxide content was 32.8 milliequiv. per liter on August 11. On August 13 the arterial-blood carbon dioxide content was 25.9 milliequiv. per liter, the pH was 7.45, and the oxygen saturation at rest was 93.6 per cent. The circulation time was 12 or 13 seconds, and the venous pressure was equivalent to 18.5 cm. of water. An electrocardiogram was within normal limits and indicated vertical heart position. Routine posteroanterior roentgenograms of the chest taken on admission and 1 week later are shown in Figure 6. A film taken on August 12 (Fig. 6*A*) was interpreted as showing emphysema of both lungs, most marked in the right lower lobe. The 2d film, taken on August 19 (Fig. 6*B*), showed a return of the right leaf of the diaphragm to a normal position, with a considerable decrease in the basal emphysema. The expirogram (Fig. 3) showed great slowing of expiration, worse during forced expiration and partially relieved by bronchodilators.

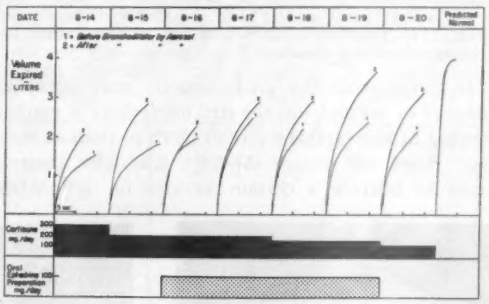
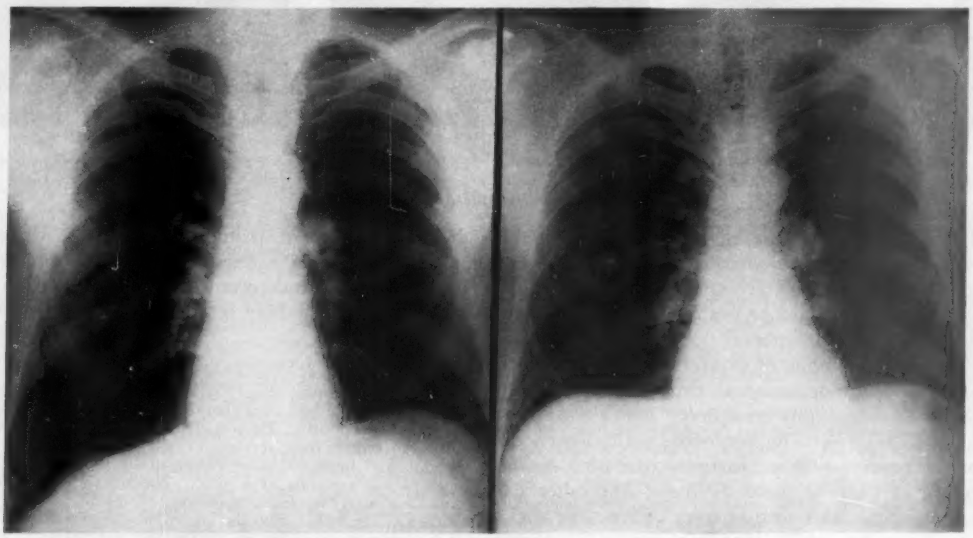


FIGURE 7. *Effect of Treatment on the Expirogram in Case 2.*



A B

FIGURE 6. *Posteroanterior Roentgenograms in Case 2.*

The film taken before treatment with cortisone (A) *shows radiolucency and depression of the diaphragm, most noticeably on the right.*

The film taken after five days of treatment with cortisone (B) *shows return of the right leaf of the diaphragm to a normal position.*

The patient was treated with cortisone and a preparation containing ephedrine, aminophylline and potassium iodide

(Fig. 7). Because of urinary frequency this preparation was discontinued after a few days. He improved so much that he could climb a flight of stairs with little dyspnea whereas on admission even the exertion associated with dressing himself caused distress.

Objective evidence of improvement is provided by the expirograms in Figure 7. Although the rate of expiration was still abnormal on August 19 (1350 cc. or 40 per cent of a predicted normal volume of 3360 cc. in the 1st second), it was 170 per cent greater than it had been before treatment. The pulmonary-function studies in this patient are described in detail elsewhere.[19]

In emphysema the vital capacity may be either reduced or normal, but the striking feature is marked slowing of the expiratory rate, more so than in asthma. Since this disease develops gradually, patients learn to tolerate a certain amount of dysfunction and do not usually seek medical relief until the slope of the expirogram is noticeably reduced. Indeed, those whom we have studied expired, within the first second, a third or less of the predicted normal volume for that interval. A considerable slowing from the beginning of expiration in the presence of a relatively normal vital capacity is probably pathognomonic of this condition. The abnormality is at best only partially reversible with bronchodilators. The reversibility has been attributed to the presence of bronchospasm by some, but other explanations have also been offered. Even very slight dilatation by relaxation of existing normal muscular tone, decrease of edema or both, in an airway already narrowed by the pathologic process, may permit relatively large increases in airflow. Conversely, very slight narrowing produced by an opposite change in the bronchial wall no greater than that occurring in normal persons might cause a striking increase in resistance to airflow. This may explain the marked susceptibility of patients with emphysema to inhaled aerosols of histamine without invoking the specific reactivity of the bronchial tree that appears to be present in bronchial asthma. In emphysema, unlike asthma, there is always a gross irreversible residual defect, even after the most vigorous treatment.

As mentioned above, if expiration is performed slowly, the volume expired is often greater than that with rapid expiration. Surprisingly enough the rate of expiration may be just as fast as or faster than that when maximal effort is made. This phenomenon has been attributed to collapse of poorly supported airways during forced expiration.

Senile Emphysema

Many patients who present the thoracic deformity commonly associated with emphysema do not have clinically significant pulmonary disease. Although labeled "senile emphysema" these cases are associated with a chest deformity that limits the motion of the thoracic cage but interferes little with respiration.

A B C

Figure 8. *Front* (A) *and Side* (B) *Views of the Thorax, with a Posteroanterior Film of the Chest* (C) *in Case 3, a Patient with Senile Emphysema.*

Case 3. T.F., a 75-year-old man, was admitted to the hospital on November 26, 1954. An epidermoid carcinoma of the right tonsil had been removed, and the area irradiated four years previously. He was then well until 1 year before admission, when food seemed to stick at the level of the xiphoid, and he found it necessary to chew thoroughly and to eat small amounts at a time. Narrowing of the lower esophagus was demonstrated roentgenologically, and esophagoscopy revealed a fibrotic lesion of the distal end that on biopsy proved to be an epidermoid carcinoma. There had been a 13.6-kg. (30-pound) weight loss in 3 years, but there were no respiratory symptoms.

The patient had the general appearance and chest deformity shown in Figure 8*A* and *B*. Positive physical findings included bilateral cataracts and arcus senilis. The mouth was edentulous. The right tonsillar fossa was deep, and the tonsil absent. There was radiation atrophy over the right lateral aspect of the neck, and there were large, movable lymph nodes in the right supraclavicular fossa. The lungs were hyper-resonant to percussion; there were no rales or wheezes. The heart was not remarkable, nor was the rest of the physical examination. X-ray examination of the chest (Fig. 8*C*) was interpreted as showing pulmonary fibrosis, emphysema and inactive tuberculosis in the region of the right apex. An electrocardiogram was normal. There

were no chemical or morphologic abnormalities in the blood or urine.

Because of the chest deformity the surgical service requested an evaluation of pulmonary function. Although the vital capacity was reduced, the expirogram (Fig. 9) showed the expiratory rate to be normal, and there was no change with bronchodilators, sufficient evidence that the patient did not have obstructive emphysema. Therefore, an operation to remove the carcinoma of the esophagus was not considered to be contraindicated. The patient underwent esophagectomy with esophagogastric anastomosis without difficulty and had a good postoperative course.

Pulmonary Fibrosis

Pulmonary fibrosis is not a single entity. Complex disturbances occur, depending on what intrapulmonary structures are involved (bronchial, parenchymal, vascular or interstitial). Even when the main abnormality is widespread, diffuse interstitial fibrosis, such as that seen in beryllosis and scleroderma, which may be accompanied by a marked disturbance in diffusion of gases between alveoli and blood, there is usually a ventilatory disturbance manifested by abnormalities in the expirogram that may provide a useful index of the disease less costly and in some cases more useful than x-ray study. Indeed, the amount of infiltration seen on x-ray examination is an unreliable index of functional disturbance, and if one relies on this procedure alone adequate information by which to judge the clinical significance or the progress of the disease may not be obtained. Some of these points are illustrated by the following cases.

Case 4. S.H., a 49-year-old housewife, had a nonproductive cough in August, 1952, that worsened in the spring of 1953 and was then associated with shortness of breath. A routine photofluorogram of the chest taken in 1951 was reported to the patient as showing an abnormality that was not significant. A pre-employment roentgenogram of the chest in April, 1952, showed pulmonary fibrosis and caused the patient to consult a health-department clinic, where a tuberculin test was done and found to be negative, and sputum and gastric washings were negative for acid-fast bacilli. Because of progressive dyspnea she was admitted to the hospital on June 15, when physical examination was not remarkable except for rales at the bases. A roentgenogram of the chest is presented in Figure 10. A lung biopsy showed multiple granulomas of the right lower lobe, with acute and chronic pneumonitis, fibrosis and bronchiolectasis. Acid-fast stains were negative, and the process was regarded as consistent with sarcoidosis.

Treatment with cortisone, 200 mg. daily, was started on July 3, 1953. The vital capacity, initially 1350 cc., rose to 1700 cc. after 5 days of treatment. She improved greatly; both dyspnea and cough decreased, and she was able to return to work. Activity that had formerly produced dyspnea now caused no difficulty, and she has been maintained for the past 2 years on 50 mg. of cortisone daily. The initial expirograms and those obtained almost two years later are shown in Figure 11. On x-ray study questionable clearing was observed (Fig. 10).

Case 5. H.N., a 43-year-old single bookkeeper, had first noticed a cough at the age of 28 that was productive of a small amount of mucoid sputum. X-ray study of the chest 2 years later revealed mottled densities of both upper-lung fields, with increased hilar shadows. Despite negative sputum examination the diagnosis of probable pulmonary tuberculosis, with infiltration and multiple cavitation, was made at another hospital, and he was transferred to a tuberculosis sanatorium for 3 months, during which repeated sputum examinations were negative for acid-fast bacilli and there was no change in the x-ray appearance of the chest. At the age of 35 he was admitted to another hospital, where he was observed to have rales and bronchial breathing over the upper-lung fields posteriorly. Routine blood and urine examination was normal. A tuberculin test with 2d-strength PPD was negative. The vital capacity was 1600 cc. On the basis of typical x-ray findings he was

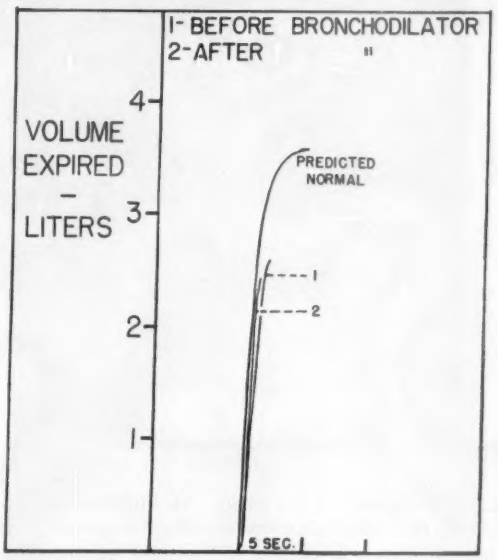


Figure 9. *Expirogram in Case 3 on December 4, 1954. This patient, a seventy-five-year-old man with senile emphysema, was 170 cm. (5 feet, 7 inches) tall.*

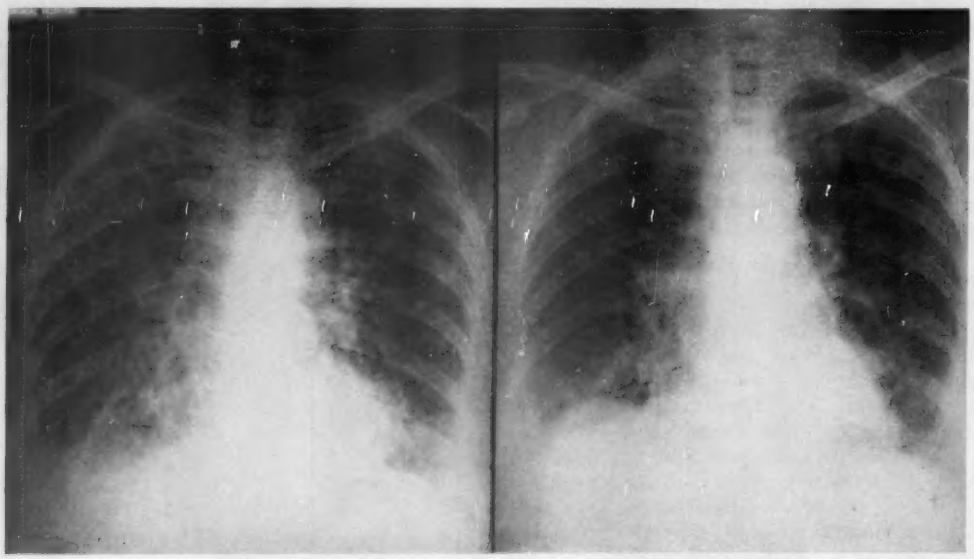
believed to have fibrocystic disease of the lungs. During the next few years his condition deteriorated; his weight fell from 54.9 kg. (121 pounds) to 44.9 kg. (99 pounds), and he became so dyspneic that he could no longer continue his sedentary work.

On April 26, 1950, he was admitted to this hospital. There were bilateral inspiratory and expiratory wheezes and fine rales at the bases. X-ray examination (Fig. 12) showed marked generalized fibrosis of both lungs, with several large cysts in the right lower and left upper lobes and numerous widely distributed small cystic areas. He was treated with cortisone, 200 mg. daily, and improved. Expirograms on April 14, 1950, just before treatment with cortisone and those on April 22, after cortisone had been given for 7 days, are shown in Figure 11. There was no significant change in the x-ray appearance of the chest, although he felt greatly improved at this point and was able to be discharged from the hospital and return to work. He was maintained on cortisone therapy for the next several years, during which he remained active at work. It was impossible to reduce the daily dosage below 75 mg. When respiratory infection developed he became dyspneic and was often hospitalized. In 1953 his condition deteriorated so that even with full doses of cortisone he was quite dyspneic. Severe osteoporosis and severe compression fractures of the spine that caused severe pain ultimately developed. He died in March, 1955. Autopsy revealed severe fibrosis and bullous emphysema of both lungs, marked osteoporosis and adrenal atrophy.

The expirograms in Case 4, the patient with sarcoidosis (Fig. 11), demonstrated considerable restric-

tion of lung excursion so that a small volume was expired. The initial rate was relatively rapid, indicating the absence of bronchial obstruction, but there was slowing of the terminal portion, presumably because of rigidity of the lungs. No improvement followed the administration of bronchodilators. The tracing obtained after many months of treatment with cortisone showed marked objective improvement, and the patient was subjectively much improved. Subjective improvement was more easily confirmed with the expirogram than with x-ray study, which, although it showed some clearing, was not strikingly different from that obtained before treatment.

When fibrosis is primarily in relation to the bronchioles, emphysema with its characteristic curve is produced. The expirograms in Case 5, the patient with idiopathic fibrosis (Fig. 11), illustrate this point. The expiratory rate was slowed, and there was some improvement with bronchodilators before treatment with cortisone. Further improvement followed cortisone therapy. The change in the expirogram in this case was accompanied by subjective improvement, but this was not reflected in the x-ray film.



A B

FIGURE 10. *Posteroanterior Roentgenograms of the Chest in Case 4, Showing Diffuse Infiltration before Treatment with Cortisone* (A) *and Some Clearing Twenty-One Months Later* (B).

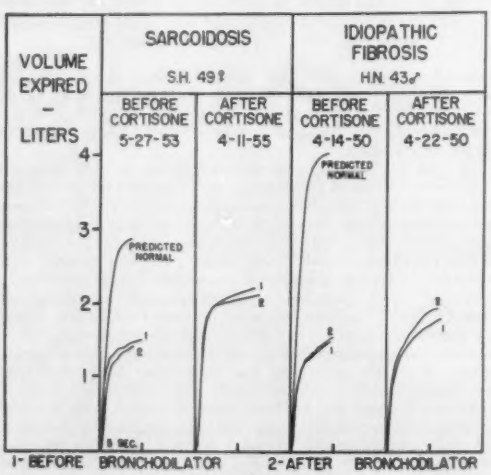


FIGURE 11. *Expirograms in Case 4 (Sarcoidosis) and Case 5 (Pulmonary Fibrosis), before and after Treatment.*

The cases reported above illustrate the usefulness of the expirogram in evaluating patients with diffuse pulmonary infiltration. We have not had enough experience with this type of patient to be able to state the relative value of this test compared with more complex methods of measuring pulmonary function. That the expirogram is more sensitive than the x-ray film in revealing small changes seems quite apparent. This is important because it is often impossible to state how much of the pulmonary opacity seen on x-ray examination is due to reversible pulmonary inflammation rather than fibrosis.

DISCUSSION

Because one of the most important characteristics of a disease is its course, a simple test, often repeated, may give more information than a more elaborate study that is expensive or difficult to perform and hence done only rarely. A disadvantage of tests of pulmonary function in general is the requirement

that the patient tolerate a tightly fitting mouthpiece and nose clip. If, in addition, the procedure is prolonged, measurement of the patient's functional capacity will be difficult or impossible in those who are unco-operative or in pain, or who feel ill. For clinical purposes it is highly desirable to place as few demands on the patient as possible. For this reason, we regard the expirogram, which is easily obtained and informative, as a most useful procedure.

The maximum breathing capacity widely used as a test in obstructive respiratory disease has, in our opinion, the disadvantages outlined above. The exertion required may actually provoke asthma, and patients with emphysema are often observed to have greater ventilation during exercise than when deliberately trying to breath maximally. Thus, the maximum breathing capacity is least accurate in diseases characterized by bronchial obstruction, in which a test that takes into account the rate of airflow is most necessary. Furthermore, co-ordination, motivation and familiarity with the procedure affect the result and lead to variations that do not necessarily reflect the patient's pulmonary function. Although these factors also affect the results obtained with the expirogram, a test that is less difficult for the patient is much less likely to fail in this respect. The slope of the expirogram is a measure similar to the maximum breathing capacity so far as functional capacity goes and seems to be a more reproducible measurement. In consequence, smaller changes become significant. Therefore, the expirogram not only demands less from the patient but also is more useful in following the course of his disease.

There are several reasons why we believe that a tracing has an important advantage over the timed capacity in which the amount expired in one, two or three seconds is recorded by means of an interval timer,[4] in addition to the total vital capacity. More can be learned from the slope throughout the period of expiration than from volumes measured at arbitrary intervals. In obstructive disease, for example, expiration is greatly slowed from the beginning, whereas in chronic heart failure and pulmonary fibrosis a pronounced decrease in slope occurs only at the terminal portion of the curve. Thus, on the basis of the one-second capacity and the total vital capacity alone, one could not distinguish the curve of acute heart failure from that of chronic failure or fibrosis, and, on the basis of the three-second and total capacity, one could not distinguish emphysema from chronic failure and fibrosis. Furthermore, errors in the performance of the tests, otherwise difficult to detect, can be readily recognized from a tracing. For example, leakage from the nose or around the mouthpiece produces a characteristic flattening of the terminal portion that one learns to recognize. This occurs most often in patients with interfering dentures. Failure to exert a maximal effort may produce an irregular pattern, or, if the patient terminates his effort prematurely, the characteristic terminal curvature may be missing. A tracing becomes especially valuable in very sick patients who have difficulty in co-operating. Even if the entire tracing is not satisfactory, one may get useful information from a segment of it. Finally, the tracing provides a permanent record, which may be carefully compared with subsequent tracings. A recently published work on the lung[5] points out the characteristics of the spirogram recorded on a rapidly moving kymograph in various lung disorders. This method enables one to analyze inspiration as well as expiration and to place the tracings in relation to the patient's normal tidal excursion. We realize that valuable information can be obtained with this technic that cannot be obtained from the expirogram. However, most of the important changes in pulmonary disease are more marked during expiration, and there are several considerations that make the expirogram more applicable to general clinical use. Because the patient never inhales from the apparatus in the performance of an expirogram, the spirometer need not be cleaned after use by a patient with communicable respiratory disease. No valves are required, and the patient need not suffer the inconvenience and discomfort of a nose clip and tightly fitting mouthpiece. Perhaps for this reason we find that patients occasionally have a larger vital capacity when simply blowing into a tube than when a closed system with valves is used. Since overlapping of the

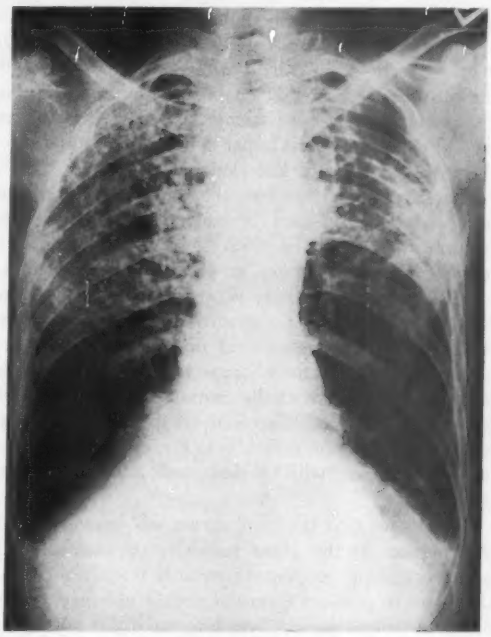


FIGURE 12. *Posteroanterior Roentgenogram of the Chest in Case 5, Showing Generalized Fibrosis and Multiple Cystic Areas.*

individual expiratory curve creates no difficulty in measurement or interpretation, several efforts can be recorded on a single sheet of typewriter paper fastened to the drum with scotch tape. This can then be removed and made part of the patient's record.

There are various ways of classifying and testing lung function. Generally, one considers ventilation—the movement of air in and out of the lung; distribution of air within the lung; and diffusion—the transfer of gases from the alveolar spaces to the capillaries. There are a great many tests that have been devised to measure various aspects of each of these functions and that enable pulmonary physiologists to characterize a patient's disorder with a great deal of accuracy. This paper contributes little if anything to this fund of knowledge.

Practically all disorders that diffusely affect the lung, whether primary or secondary, produce important changes in the ability of a patient to exhale forcibly. These changes are most characteristic in conditions in which there is obstruction to the bronchial tree. However, conditions that affect the rigidity of the lungs such as fibrosis and congestive heart failure also cause changes in the expirogram, as do diseases that restrict the motion of the chest. This is true even in conditions that are primarily vascular or produce diffusion difficulties. The changes observed in heart disease will be discussed more fully elsewhere.[1]

We believe that the expirogram will provide useful information in the great majority of cases of pulmonary disease or dyspnea even if it only serves in the latter to rule out a ventilatory disturbance. If the disorder is primarily ventilatory, little additional clinically useful information can be obtained from more complicated ventilatory measurements. Occasionally, measurement of intrapulmonary gas distribution may be required. Patients with pulmonary disease so advanced as to preclude satisfactory performance of the expirogram will also be unable to tolerate other studies of ventilatory function, and the progress of their illness is usually best followed at this stage by blood-gas analysis. In patients who have a disturbance of pulmonary circulation or of alveolar-capillary diffusion, the expirogram or other measurements of ventilation may fail adequately to reflect the respiratory disturbance. However, in patients with clinically evident pulmonary disease, a normal or nearly normal expirogram will immediately suggest a significant respiratory defect, which may then be defined with appropriate tests.

Summary and Conclusions

The expirogram, a tracing made on a rapidly moving kymograph during the performance of the vital capacity, is presented as an easily performed test of pulmonary function giving a great deal of information of practical value in the management of patients with respiratory disease. It requires equipment that is no more expensive than that designed to measure the basic metabolic rate. It should therefore be practical to carry out this test not only in hospitals but also in the office, especially of those whose primary interest is pulmonary and cardiac disease.

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CLINICAL APPLICATION OF COBALT^{60}-LABELED VITAMIN B_{12} URINE TEST*

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SCHILLING[1] has observed that normal patients excrete definite amounts of radioactive substances in the urine after an oral dose of 2 microgm. of vitamin B_{12} labeled with cobalt^{60} and a parenteral "flushing" dose of 1000 microgm. of the nonradioactive vitamin B_{12}. In contrast, patients with pernicious anemia in remission excrete no detectable radioactivity in the urine when the labeled vitamin is administered with water or boiled gastric juice. However, the simultaneous administration of active gastric juice with the oral dose of vitamin B_{12} labeled with cobalt^{60} results in easily detectable amounts of radioactive substances in the urine. More recently, Schilling[2] has specified the range of excretion in normal subjects as 7 to 21 per cent, that in patients with pernicious anemia as 0 to 2.3 per cent, and that in

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subjects with histamine-fast achlorhydria as 3.2 to 29.6 per cent in the first twenty-four-hour sample of urine.

The purpose of this report is to describe our experience with the clinical application of the cobalt^{60}-labeled vitamin B_{12} urine test in a varied group of patients. Because of classification difficulties in problem cases, a modification of the original technic has been added during the course of this study.

Methods

Three lots of cobalt^{60}-labeled vitamin B_{12}* having specific activities of 214, 214, 189 microcuries per milligram respectively were used as the tracer. Doses containing 0.6 microcuries of radiocobalt were mixed with water to a volume of 100 cc., of which 1 cc. was used as a standard to determine the radioactivity of the "drink," and 99 cc. was given to the patient. Schilling's[1] technic was followed except for the counting procedure, in which 2-cc. and 4-cc. samples of urine specimen were counted for five minutes in a well-type scintillation counter. This is referred to below as the direct method.

The modification used consisted of concentrating the total twenty-four-hour volume by rapid evaporation to a volume less than 200 cc. Foaming was prevented by a small amount of silicone defoamer (Antifoam A).† Thirty-minute counts of 4-cc. aliquots of the concentrated urine and of the standard were obtained, and from these the percentage of orally administered radioactive substances in the twenty-four-hour urine was calculated (concentrated method). Studies of the distillates revealed no radioactivity. The twenty-four-hour concentrates of 3 normal persons not tested by the method employing cobalt^{60}-labeled vitamin B_{12} yielded 228, 261 and 388 counts per minute above background (naturally present).‡ This number of net counts is equivalent to approximately 0.05 per cent of the oral dose.

Estimates of standard error for 2-cc. and 4-cc. samples of urine counted directly (without concentration) for five minutes were approximately 15 and 9 per cent respectively. In contrast, the standard error of the concentrated urine counted for thirty minutes was less than 1.0 per cent.

Attempts were made to determine the radioactivity of stool samples and of the total body by means of the sodium iodide crystal method.[3] The results were unsatisfactory.

Results

The 36 patients studied are listed in Table 1, and

*Kindly supplied by Merck and Company, Rahway, New Jersey, under the terms of the *General Authorization for Human Use*, delegated to The University of Chicago Clinics by the Isotope Division, United States Atomic Energy Commission.

†Available from Dow-Corning Corporation, Midland, Michigan.

‡Most of this radioactivity was undoubtedly due to the naturally occurring radioactive potassium (K^{40}). This number of counts represents about 70 microgm. of K^{40} per twenty-four hours.

Table 1. *Amounts of Radioactivity Excreted by Normal Subjects and Patients with Various Conditions.*

	Case No.	Patient	Age	Radioactivity Recovered in 24-Hr. Urine	
				Direct	Concentrated
			yr.	%	%
Normal subjects:	1	L.L.	67	7.9	
	2	L.D.	72	10.0	12.0
	3	A.D.	58	12.0	10.0
Patients with pernicious anemia:	4	E.G.	36	1.0	
	5	A.J.	46	0.1	
	6	E.F.	50	0.9	0.07
	7	E.F.	64	0.	0.
	8	F.K.	63	0.1 9.5*	0.2 5.5*
	9	L.B.	41	0.5	0.8
	10	I.M.	50	0.9	0.04
Patients with megaloblastic anemia other than pernicious anemia:	11	A.O.	44	7.1	
	12	R.C.	30	0 0 0*	0*
Patients with dorsolateral spinal neuropathy:	13	J.R.	48	2.6	
	14	S.W.	68	1.6	.05
Patients with achlorhydria:	15	A.G.	44	7.8 5.5	5.1
	16	O.H.	58	2.8 1.6	1.9
	17	G.J.	76	3.6 1.6	
	18	F.B.	50	8.8	
	19	P.V.	59	10.0	
	20	W.G.	67	9.1	
	21	G.P.	52	6.8	
	22	M.N.	52	5.9	
	23	V.S.	61	3.6	
	24	J.W.	56	6.7	7.2
	25	F.R.	42	1.4	2.1
	26	W.S.	65	0.4	0.6
	27	K.R.	62	4.1	4.3
Patients with gastric carcinoma	28	A.J.	68	5.9	
	29	J.G.	61	9.1	
	30	S.B.	62	2.8	
	31	S.D.	76	0.5	0.4
Patients with gastric resection: Subtotal:	32	H.J.	77	1.4	
	33	H.M.	55	6.1	7.3
Near total	34	A.J.	68	1.7	1.8
Total	35	E.A.	65	0.5	
	36	F.N.	80	0 14.0*	0.1 13.4*
Patients with fish tapeworm:	37	I.K.	42	8.5	8.4

*Potent intrinsic factor, 5 mg., added.

the results are recorded. The 3 normal subjects exhibited a normal output of hydrochloric acid by gastric analysis, and no gastrointestinal lesions were demonstrated by x-ray examination. They excreted 7.9, 10 and 12 per cent of the dose, respectively.

Pernicious Anemia

All 7 patients with pernicious anemia excreted less than 1.0 per cent of the oral dose as determined by either method. Five of these were examined during relapse, and the typical hematologic response was observed after the administration of vitamin B_{12}. Case 8, who had previously had the diagnosis of pernicious anemia established at this hospital, discontinued liver therapy seven years earlier, and the first symptoms of relapse developed a month before admission. He denied the ingestion of any medication, including vitamins, during this period. The administration of potent intrinsic factor* increased the urinary excretion from less than 1.0 to 5.5 per cent. Case 9, a patient with known acquired agammaglobulinemia since 1947, manifested an anemia that was identified as pernicious anemia. The recently reported cases of acquired agammaglobulinemia have not yielded evidence of pernicious anemia.[4-6]

Megaloblastic Anemia Other than Pernicious Anemia

Two patients with megaloblastic anemia were studied. Case 11,† a chronic alcoholic patient, was found to have a macrocytic anemia, a histamine-fast achlorhydria and a normal stomach at gastroscopy. A sternal-marrow aspiration was interpreted as showing pernicious anemia in early relapse complicated by neoplasm or infection. On liver biopsy fatty cirrhosis, moderately advanced and active, was reported. The patient was treated by liver extract parenterally. Seven months later the test with cobalt^{60}-labeled vitamin B_{12} was performed in this hospital when his hemogram was low normal. He had not been given intrinsic factor by mouth, and, in addition, he had been hospitalized fifteen hours earlier, thereby excluding a false-negative test owing to the intake of exogenous intrinsic-factor therapy within twelve hours of study. Thus, the excretion of 7.1 per cent of the radioactive substance given by mouth appears to be valid evidence that he did not have pernicious anemia. Three months later he was hospitalized elsewhere because of jaundice and edema. A macrocytic anemia was treated with vitamin B_{12}. Hepatic coma developed, and he died two weeks later. Post-mortem examination disclosed portal cirrhosis of the liver, with marked fatty metamorphosis and focal necrosis. Erythroid hyperplasia of the bone marrow was found. Microscopical sections of the gastric mucosa were not obtained. Presumably, this represents a case of megaloblastic anemia secondary to liver disease with normal intrinsic-factor activity as measured by the test with cobalt^{60}-labeled vitamin B_{12}.

Case 12 had had multiple small-bowel resections for regional enteritis, with the subsequent development of a macrocytic anemia. The bone-marrow aspiration was interpreted as indicating megaloblastic anemia. After the administration of vitamin B_{12} parenterally, a 23 per cent reticulocyte response and a normal hemogram were observed. The presence of hyperchlorhydria and a normal mucosa of the gastric fundus by biopsy excluded the possibility of pernicious anemia. Two separate tests with cobalt^{60}-labeled vitamin B_{12} were performed, and no radioactivity was observed in the urine. A third test, with the simultaneous administration of 5 mg. of potent intrinsic factor, demonstrated no urinary radioactivity. The intrinsic-factor material was found to be active by study of a patient with pernicious anemia (Case 8) and another with a total gastrectomy (Case 36). The megaloblastic anemia in Case 12 was apparently due to the impaired absorption of extrinsic factor secondary to the massive small-bowel resection.

Dorsolateral Spinal Neuropathy

Two patients had neurologic findings consistent with the diagnosis of posterolateral sclerosis, but had normal hemograms. Case 13 had taken unidentified vitamin tablets for several months before entry, which may have obscured the hematologic findings. Achlorhydria and marked diffuse atrophic gastritis were found at gastroscopy. In Case 14 the diagnosis had been made seven years earlier, when achlorhydria and a normal sternal-marrow aspiration were found. After liver therapy both patients improved greatly with minimal residual neurologic changes. The discrepancy of excretion values in Case 14 by the two methods is noteworthy. We believe that the results obtained with the concentrated specimen are more reliable than those found with the direct method.

Achlorhydria

Thirteen patients with achlorhydria were examined, and 5 unexpected results encountered. Case 15, examined a year after the first study, exhibited a 30 per cent decrease in excretion; further studies at intervals may show fluctuating variations or a gradual decline anticipating the development of pernicious anemia. Case 16, a patient known to have achlorhydria and diffuse atrophic gastritis by gastroscopy for eight years, demonstrated a normal hemogram and bone marrow at the time of study. He ate approximately 0.5 kg. (1 pound) of broiled liver a week for many years but did not take vitamins. Five years earlier, during an investigative study, he had received several injections of liver extract, but none since. He excreted 2.8 per cent of

*Kindly supplied by Merck and Company, Rahway, New Jersey.

†We are indebted to Dr. Steven Schwartz, of the Department of Hematology, Cook County Hospital, for permission to study this patient.

the radioactive substance by the direct method and eleven months later yielded 1.6 per cent (direct) and 1.9 per cent (concentrated). The reduction by 42 per cent (direct) over an eleven-month period may not be significant; however, the question may be raised, Is this a patient with pre-pernicious anemia?

Case 17 was found to have a hemoglobin of 11.7 gm. per 100 cc. and a red-cell count of 3,130,000, and a sternal-marrow aspiration interpreted as not characteristic of pernicious anemia. Two separate tests were performed at an interval of eight days with a 50 per cent discrepancy of results. It is probable that the second testing was influenced by some blocking action of the first, although a counting error (direct) may have caused the difference.

Case 25, a patient with diabetes mellitus, had mild macrocytic anemia, with evidence of diffuse neurologic damage, including posterolateral sclerosis. A bone-marrow aspiration was interpreted as not typical of pernicious anemia. After vitamin B_{12} therapy a reticulocytosis was not observed. The difference between the 1.4 per cent found by the direct and the 2.1 per cent by the concentrated method is probably not significant, but the latter value is considered the more reliable.

Case 26, a patient with diabetes mellitus, arteriosclerotic heart disease and compensated congestive heart failure had normal neurologic and hematologic findings, including a bone-marrow examination. The blood urea nitrogen was 20.5 mg. per 100 cc. No previous liver or vitamin therapy had been administered. The insignificant radioactivity detected in the urine by both methods justifies a diagnosis of a pernicious anemia. Unfortunately, a repeat study could not be performed. The question may be raised whether this patient has pernicious anemia before the development of clinical symptoms.

Gastric Carcinoma

Four cases of gastric carcinoma were studied; 3 patients with discrete lesions excreted significant amounts of radioactive substances. Case 31, with no history of pernicious anemia, exhibited a normal hemogram and a nonmegaloblastic bone-marrow aspirate. At operation a diffusely infiltrating gastric tumor extending from the pylorus to the cardia was found. The preoperative values of excretion, by both methods, were consistent with a pernicious-anemia state. Thus, the test with cobalt^{60}-labeled vitamin B_{12} suggested a diagnosis of pernicious anemia whereas no clinical evidence supported this diagnosis.

Gastric Resection

Of 5 patients who had had a previous gastric resection, 2 with total gastrectomy demonstrated no radioactivity in the urine test. Case 32 had a subtotal resection for a localized gastric carcinoma, with no previous history of or evidence for pernicious anemia except achlorhydria. The small value excreted, 1.4 per cent, makes this a case of pernicious anemia. Case 33 had a subtotal gastric resection for a benign polyp and also had achlorhydria before surgery. His excretion of the labeled vitamin was within the range of normal. Case 34 (the same patient as Case 28) had 90 per cent of the stomach resected for a polypoid carcinoma. At the time of the second test, five months after the first, the excretion value had fallen from 5.9 to 1.7 per cent.

Fish Tapeworm

One patient (Case 37) with a fish-tapeworm *(Diphyllobothrium latum)* infestation was examined before antihelminthic therapy. The hemogram and bone marrow were normal. The percentage of radioactive material excreted in the urine was in the normal range, thus indicating that the presence of the parasite does not prevent the absorption of vitamin B_{12}. It is of interest that washed sections of the worm, after purging, contained small amounts of radioactivity; 236, 973 and 153 net counts per minute were obtained from 3-cm. segments of neck and mature and gravid proglottids respectively counted in a well-scintillation counter for five minutes. The suspending fluid of each specimen revealed no radioactivity.

Conclusions

From this study it is apparent that a spectrum of values for the percentage of radioactive material in the urine may be obtained by the cobalt^{60}-labeled vitamin B_{12} test. The cases at both extremes appear clearly defined regardless of whether the urine is counted directly or is concentrated. However, patients presenting equivocal values in the range of 1.0 to 2.6 per cent remain without a diagnosis and represent inability of the technic to discriminate subjects capable of absorbing the vitamin in adequate amounts from those who cannot do so. To overcome this difficulty, which was due in fact to the small number of counts, the concentrated method has been adopted. By reducing the volume to be tested, and prolonging the counting period, one can achieve a greater statistical accuracy.

Insignificant values for radioactive substance in the urine — that is, less than 1.0 per cent — were observed in patients with pernicious anemia and those with total gastrectomy, as previously reported by Schilling. It is of interest that similarly low values were found in 3 additional patients. One patient (Case 12) failed to absorb the labeled vitamin, whether administered with or without potent intrinsic factor, owing to a massive small-bowel resection. A second patient (Case 31) had a diffuse gastric carcinoma, without other evidence of pernicious anemia. The recovery of significant amounts of radioactive substances in the urine of 2 patients

with gastric carcinoma seems to exclude the carcinoma per se as the cause of this defect. It may be postulated, however, that the carcinomatous infiltration destroyed the intrinsic-factor production sites, with the resultant failure of absorption. The third case (Case 26) remains unexplained at this time pending further studies; prolonged observation without treatment will be necessary to test the hypothesis that this patient is in the latent period of pernicious anemia.

The clinical value of the test is recognized. However, further experience must be obtained to define the accuracy and limitations of this technic in clinical practice.

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THE NONTOXIC NODULAR HYPERPLASTIC GOITER

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BOSTON

RECENT studies on sporadic goitrous cretinism[1-5] have called attention to the interesting paradox of hypothyroidism associated with a hyperplastic nodular goiter. These studies have demonstrated an intrinsic defect within the thyroid gland in its synthesis of thyroid hormone that can occur at different stages, either in the binding of iodine to tyrosine or in the conversion of diiodotyrosine to thyroxin. Furthermore, judging by the different degrees of hypothyroidism in cretins, the defect in hormone synthesis may be either partial or complete. Spontaneous return of thyroid function to normal and the rarer occurrence of hyperthyroidism[6] in some cretins suggest the possibility that the deficiency is even reversible.

The goiter is believed to be a compensatory hyperplasia produced by pituitary thyrotropic stimulation in response to a low circulating thyroxin level. Such goiters vary widely in size and show a varied microscopical picture, which includes diffuse epithelial hyperplasia, small follicles, scanty colloid and fetal, embryonal or colloid adenomas.[7-9]

In view of the different degrees of faulty hormone synthesis seen in cretins, it is quite possible that minor degrees of the same deficiency account for the presence of hyperplastic nodular goiters in patients who are not cretins. The following case of nontoxic nodular hyperplastic goiter occurring in a normal adult is presented as a variant of goitrous cretinism.

Case Reports

Case 1. A 29-year-old male schoolteacher registered at the clinic on January 4, 1955, complaining of recurrent goiter of 15 months' duration. The family history revealed that a sister had had thyroidectomies performed at 21 years and at 23 years of age for nontoxic goiter. The patient's goiter had first appeared at the age of 10 years. There was no change in its size until the age of 23, and from then on it enlarged steadily. On October 13, 1953, when the basal metabolic rate was +5 per cent, a subtotal lobectomy on the right and a total lobectomy on the left were done elsewhere. The pathological report was follicular hyperplasia and benign embryonal adenoma of the thyroid gland. Eight months after operation the goiter recurred and enlarged steadily thereafter.

Physical examination showed bilateral enlargement of the thyroid gland that was more prominent in the right lobe and isthmus. There was no evidence of myxedema or hyperthyroidism. The basal metabolic rate was −16 per cent; the blood cholesterol was 130 mg., the serum protein-bound iodine 4 microgm., and the total serum iodine 5 microgm. per 100 cc.

The thyroidal uptake of I^{131} (50 microcuries) was rapid, reaching 78 per cent in 6 and 83 per cent in 24 hours. The administration of 2 gm. of potassium thiocyanate, 7 hours after the tracer dose, did not cause a discharge of iodine from the gland (Fig. 1). These observations indicate an increased avidity of the gland for iodine and an ability to convert it to an organically bound form, part of which must be in the form of thyroid hormone.

On April 4 a total thyroidectomy was performed, 123 gm. of tissue being removed. The microscopical picture was that of diffuse atypical epithelial hyperplasia, with numerous small nodules (Fig. 2).

Brief summaries of 2 additional cases are included here. They appear to be the same condition although proof is lacking since iodine studies were not done.

Case 2. A 32-year-old man was first seen at the Lahey Clinic on January 9, 1952, complaining of a large recurrent goiter. The goiter had first appeared at the age of 10 and remained stationary for the next 20 years. At the age of 30 the patient consulted a surgeon because of a recent increase in its size. The basal metabolic rate at that time was −17 per cent. Subsequent thyroidectomy was performed in August, 1950. The microscopical sections revealed adenomatous goiter, with diffuse hyperplasia. Six months later the goiter recurred and steadily enlarged. In January, 1952, 17 months after the 1st thyroid operation, the patient was seen at the Lahey Clinic.

Examination revealed soft and nodular bilateral thyroid remnants, at least 6 times larger than normal. The basal metabolic rate was − 24 per cent, but there was no clinical evidence of myxedema or hyperthyroidism.

On January 10 a total thyroidectomy was done, 347 gm. of tissue being removed. The pathological diagnosis was adenomatous goiter, with atypical diffuse hyperplasia.

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†Formerly, fellow in internal medicine, Lahey Clinic.

The patient has been maintained on desiccated thyroid daily. Postoperative follow-up examinations have shown no recurrence of goiter, and the metabolic rate has ranged from −10 to −14 per cent.

CASE 3. A 32-year-old man was first seen at the Lahey Clinic on July 30, 1953, complaining of a recurrent goiter. The goiter was first detected at the age of 6 years, and subtotal thyroidectomies were performed elsewhere at the age of 9, 18 and 21 years by competent thyroid surgeons. The present recurrence appeared 3 months after the last thyroid operation (in 1942). The patient took desiccated thyroid irregularly, going as long as 2 years without the medication. He noted an increase in the size of the goiter when not taking thyroid, but felt well otherwise.

Examination revealed a diffusely enlarged, nodular thyroid gland. There was no evidence of myxedema or hyperthyroidism, and the patient showed no stigmas of childhood cretinism. The basal metabolic rate was −12 per cent.

A radical subtotal thyroidectomy was done on July 31, 1953. The surgical specimen weighed 180 gm. The pathological diagnosis was adenomatous goiter, with atypical hyperplasia.

The patient has been maintained on desiccated thyroid daily since his operation. The goiter has not recurred, and the basal metabolic rate has been normal (−2 per cent).

DISCUSSION

Goitrous cretins have given clinical evidence of hypothyroidism, with low basal metabolic rates, high blood cholesterol levels and retarded bone age. In these patients studies of uptake of radioactive iodine

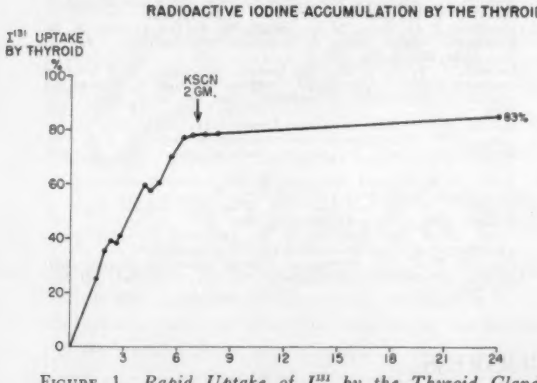

FIGURE 1. *Rapid Uptake of I^{131} by the Thyroid Gland, Showing Failure of the Gland to Discharge Iodine after Administration of Potassium Thiocyanate (KSCN).*

show a marked avidity of the thyroid gland for iodine, with a rapid uptake in the high normal or hyperthyroid range, indicating that the gland is able to trap large amounts of iodine.[10,11] Some are unable to bind iodine to tyrosine,[3-5] and others are able to convert the iodine to an organic form, which, however, is not thyroxin or triiodothyronine.[1,2,12] On the clinical side, the administration of desiccated thyroid to such goitrous cretins reduces the size of the goiter and occasionally causes it to disappear. Partial thyroidectomy in these patients is frequently followed by recurrence of the goiter.

Isolated reports by Long,[13] Poate and Macindoe[14] and Heptinstall and Porritt[15] have called attention to the occurrence of adenomatous goiters that have a marked tendency to recur repeatedly after partial thyroidectomy; these patients were children or young adults with no evidence of cretinism or myxedema. Total thyroidectomy was necessary to prevent a recurrence. The microscopical studies of these goiters revealed adenomatous changes, diffuse epithelial hyperplasia and scanty colloid. Studies with radioactive iodine were not done, but it seems likely that these cases could be considered lesser variations of the same defect that occurs in the goitrous cretins.

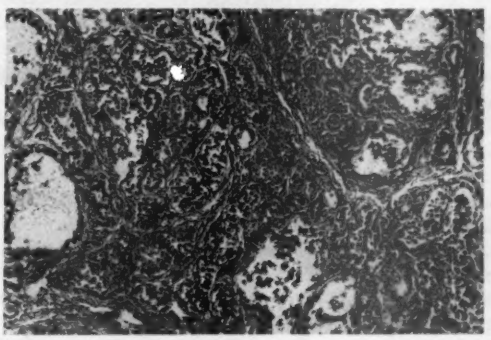

FIGURE 2. *Microscopical Section of the Thyroid Gland, Showing Diffuse Hyperplasia of an Atypical Character and Small Follicles, with Very Scanty Colloid.*

In Case 1 reported above, radioactive-iodine studies showed a rapid and high uptake of I^{131} by the thyroid gland and an ability to bind that iodine organically since there was no fall in counts over the gland after the oral administration of 2 gm. of potassium thiocyanate. The absence of clinical myxedema, the normal basal metabolic rate of −16 per cent, the blood cholesterol of 130 mg. per 100 cc. and the low-normal protein-bound iodine of the serum (4.0 microgm. per 100 cc.) indicate that the thyroid gland was producing enough thyroid hormone to avoid myxedema. The presence of a goiter that microscopically showed follicular hyperplasia suggested that output of thyroid hormone by the gland was maintained at a normal level only by constant stimulation by thyrotropic hormone. Partial thyroidectomy in this patient served only to enhance the TSH stimulus to regrowth of the thyroid remnants.

These 3 cases and those of the reports already referred to fall into a relatively constant clinical pattern. The patients are either children or young adults who are not cretinous but who are euthyroid, with basal metabolic rates in the lower normal range. The goiters appear early in life (three to ten years of age), gradually enlarge and tend to recur rapidly and repeatedly after partial thyroidectomy. Total excision of all thyroid tissue eliminates recurrences. The administration of desiccated thyroid may decrease the size of the goiter and may make it disappear completely.[7,16,17] Uptake of radioactive iodine by the thyroid gland is increased whereas the output of thyroid hormone by the gland, as judged by pro-

tein-bound iodine, basal metabolic rate and cholesterol studies, is in the low-normal range. Microscopical examination reveals diffuse epithelial hyperplasia and adenomatous changes similar to those in the thyroid glands of goitrous cretins. These characteristics suggest that the etiology of the goiter in these patients is similar qualitatively to that of goitrous cretins, differing only in the degree of the thyroid defect.

Although patients presenting these paradoxical findings are seen infrequently in a thyroid clinic, perhaps more patients with the same intrinsic thyroid defect might be found if looked for. All nontoxic nodular goiters with high I^{131} uptakes and low basal metabolic rates should be carefully scanned for possible inclusion in this group. Greer and Astwood,[16] studying 18 patients with nontoxic nodular goiters, found I^{131} uptakes greater than 50 per cent of the administered dose in 33 per cent of the group. Five of 6 patients who experienced complete disappearance of their goiters on desiccated thyroid showed high thyroidal uptakes of I^{131}. These results suggest that the glands were hyperplastic and that desiccated thyroid, by blocking thyrotropic stimulation, permitted the goiter to decrease in size. Further study of nontoxic nodular goiters seems to be indicated.

Summary and Conclusions

A case of nontoxic, nodular, hyperplastic goiter in a twenty-nine-year-old man is reported. Studies showed a radioactive-iodine uptake in the hyperthyroid range, an ability of the thyroid gland to bind iodine into an organic form and a serum protein-bound iodine in the low-normal range of 4 microgm. per 100 cc. Clinically, the patient gave no signs of cretinism, and the basal metabolic rate was in the low-normal range (−16 per cent).

Microscopical examination showed adenomatous changes and diffuse epithelial hyperplasia, similar to the findings in the thyroid glands of goitrous cretins.

Two additional cases with similar clinical findings are briefly presented. These are believed to have been the same condition, although not proved.

It is suggested that these patients have glands in which the synthesis of thyroid hormone from trapped iodine is at least partially defective. Maintenance of adequate hormone synthesis is achieved by compensatory hyperplasia of the thyroid gland induced by increased thyrotropic stimulation. The adenomatous changes are probably a result of long-continued hyperplasia.

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MEDICAL PROGRESS

TREATMENT OF MIGRAINE (Concluded)

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BOSTON

Prevention

Patients may be divided into three main groups so far as the frequency and severity of their attacks of migraine are concerned: those whose attacks are so infrequent that they may be termed an "unpleasant nuisance" but not a "serious threat" to life's normal degree of happiness; those whose attacks are occurring with such frequency or severity, or both, that family, business and social life is seriously disturbed but not completely disrupted; and those whose attacks are so frequent and severe that a state of chronic invalidism is produced and partial or complete disability results.

So far as the patients in the first group are concerned, the physician's responsibility consists mainly of providing successful relief for the individual attacks (as outlined in the previous sections of this review) and instructing the patient sufficiently in the nature of their causes to prevent progression into a more serious state. The yearly physical checkup affords a

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suitable opportunity to follow the progress of the disease. Extensive investigations, complicated regimens and multiple office visits hardly seem necessary for such patients and in fact may only serve to point up the whole problem unduly in the patient's mind.

The patients in the second group, however, deserve the physician's devoted time and attention, for not only are they already suffering considerably from their malady but also a certain percentage of them are destined to progress to serious incapacity. Such patients, furthermore, are usually of an age and in a stage of life that permit successful therapeutic manipulation. It is from this group that the physician will receive the most gratifying results for his efforts.

Patients in the last group are characterized by daily or almost daily headaches, marked physical and emotional exhaustion and a multiplicity of attendant complaints, such as joint pains, bursitis, digestive disturbances, vertigo, neurocirculatory asthenia, nervous irritability and despair. Large amounts of sedating, analgesic, vasoconstricting and, frequently, narcotic drugs are being consumed. Economic, family and social supports have gradually disintegrated, and life has settled into a barren succession of painful, hopeless, miserable days. Suicide is sometimes attempted. These unfortunate victims of migraine present a problem as great as that posed by patients suffering from chronic ulcerative colitis or rheumatoid arthritis, and will tax to the utmost the ingenuity, wisdom and patience of the physician. Their management receives separate attention below.

Therapeutic Concepts, Attitudes and Goals

It is important from the outset in prophylaxis that the physician, the patient and the patient's family have an understanding of the nature of the disease, the method of approach to the problem and the limitations and duration of treatment. All parties to the therapeutic program need to understand the following facts and behave accordingly:

> That at present there is no magic medicine or formula of treatment that universally "cures" migraine. That the patient is "not to blame" for having inherited the migraine trait. That the pain and misery of the migraine attack are very real and not "imaginary." That neither patient, doctor nor husband (or wife) should be intolerant, but rather all should work for better understanding of each other. That the patient and the family have the greater burden in therapy, and that the doctor is going to act as a friendly guide rather than as a "miracle man." That the whole program will require a considerable period, with frequent reviews of progress, temporary setbacks, changes of therapeutic signals and gradual re-education. That the most rewarding long-term therapy will be concerned with adjusting the patient's way of living to his or her capacities rather than with an endless round of medication. That the patient cannot be expected to make all the necessary adjustments overnight. That changes in psychologic attitudes become real only through actual practice rather than through verbal instruction. That there is definite hope for improvement through conscientious effort by both patient and physician, but that complete freedom from migraine is rarely achieved by any therapeutic program.

The patient, eager for quick relief, may find it difficult to grasp the concept that a major portion of success in treatment lies in his own hands. Such information may have to be imparted by the doctor in "easy installments" as treatment progresses. Successful therapy of the acute attack (as outlined above) may be a helpful wedge in gaining the patient's confidence and in relieving him of the fear of the devastation of future attacks — a fear that breeds more headaches. Several books and pamphlets written for the benefit of the layman may help some patients gain a concept of their problem.[68-71] When these books are taken home they may also act as silent ambassadors for better understanding by the patient's spouse. During the period in which the patient is "learning migraine" the use of helpful drugs seems definitely indicated. Indeed, throughout the program of treatment, various pharmaceutical and other measures (enumerated below) may well be useful. However, one should not rely on these adjuvants to the exclusion of more fundamental principles, since by themselves they usually prove to be of small worth.

Throughout the course of migraine therapy it appears to be important that the doctor see the patient at reasonably frequent intervals. It has been pointed out by Friedman[72] that success in treatment of any type bears a distinct relation to the frequency of visits to the doctor, and it is apparent from the diversified results obtained by different investigators using the same drugs that the element of enthusiasm and the personal touch imparted by the physician may be the most important ingredients in his prescription. This fact may bedevil the scientific investigator, but is grist to the mill of the physician, whose chief concern is to relieve his patient. It is suggested that in these interviews, once the complete history and physical and laboratory examinations have been satisfactorily completed, a good share of the time be devoted to learning what is going on in the patient's life rather than to endless discussion of symptoms and a retreat to more elaborate and expensive tests. The method of "following" a patient through a typical day and week end and noting hours of sleep, rest, deadlines, diet, or lack of it, personalities, commitments and so forth is apt to be fruitful. Harold Wolff has stressed the fact that each headache should "pay its way" in the interview by a rehearsal with the patient of the experiences leading up to the attack. Frequently, a question directed to the wife or husband of the patient regarding the cause of the head-

aches may reveal an avenue of approach to the problem that otherwise may long lie hidden.

A visit to the patient's home during an attack also helps one to assess its severity and nature and the patient's reaction to it, and to note its effects on the other characters in the drama. The general practitioner usually knows these things, but the internist or specialist may be left in the dark by his own "armchair" tactics. Thus the overcrowded home, the backward child, the in-laws living upstairs and the alcoholic spouse escape attention.

Since the basic concept in preventing migraine consists in fortifying the patient and lessening his burden, it is important to attend to any handicaps that the patient may have that act as a source of irritation and fatigue. Although the correction of such difficulties as anemia, menstrual disorders, refractive errors, dietary deficiencies, allergic disturbances, errors of metabolism and intercurrent infections usually does not specifically affect the course of migraine, any measure of this sort that serves to bolster the patient's resistance to stress and lessen fatigue may serve to reduce the patient's vulnerability to headache.

Errors in Living

Presented below is a list of common deviations from hygienic living that many persons may well practice with impunity but that are frequently a source of headache to the sufferer from migraine. Behind these errors in living lie attitudes in the patient that serve both to bring them about and to intensify the damage that they create. Such errors may have to be arbitrarily eliminated at first, but as treatment progresses it is important and fundamental to ultimate success for the patient to gain insight into his attitudes and personality traits that brought them about and to attempt suitable alteration. The errors are as follows:

Poor meals — skimpy breakfasts and lunches and large dinners eaten in a state of fatigue.

Irregular hours for meals. Postponing lunch for an hour may give anyone a mild headache but may produce a bad sick headache for the migraine patient.

Morning deadlines. Too little time is allowed between the rising hour and the scramble for school and the office.

Sleeping late on Saturdays, Sundays and holidays. The patient with migraine needs a good deal of sleep — but not in the morning. (Excessive cerebrovascular dilatation probably takes place, and breakfast is delayed.) Conversely, getting to bed early is important, since, to date, the only real cure for fatigue is rest.

Lack of breaks in the day. A short rest in the morning and afternoon, regularly obtained, is helpful.

Overcrowded schedules. Patients usually try to work in too many events in a day. They need to spread their activities more evenly over several days.

Failure to take proper vacations.

Failure to get away from their own children periodically.

Excessive participation in community and church activities.

Overanxiety regarding preparations for guests, shopping trips and vacations.

Long automobile trips. The migraine patient usually wishes to go the 500 miles in one day and ends up with a headache.

Acting as chairman (because nobody else will accept). Migraine patients do not delegate work to others. They do it all themselves.

Making up for lost time. As soon as the patient is over one attack, she usually rushes to repair her losses. Consequently, the next attack comes sooner.

Suffering petty wrongs in silence until they mount to unbearable heights. It would be better to settle differences while they are small.

Aiming for impossible goals and worrying when they cannot be attained.

Lack of exercise.

Lack of recreation.

Many similar deviations from healthful living might be listed that act as fuses to the migraine bomb. Some patients discover for themselves and eliminate practices that they have found by painful experience to be related to their attacks. The majority, however, either fail to recognize such factors or refuse to respect them. Whatever the physician can do to help the patient uncover, appreciate and alter such practices will in the long run be his greatest contribution to therapy. This process in each patient is an individual matter and apt to take time. Migraine patients do not like to admit, even to themselves, that they have any limitations. When given a regimen to follow, they are apt to adhere to the details of drug therapy to the letter but to forget the afternoon rests, reduction of an overactive social or business program and correction of poor dietary, work and sleep habits. They must be brought back gently but firmly to these fundamentals. Lennox has said that "the main reliance must be placed on the gradual education of the patient so that he will adjust his work and his methods of living to the personality and the nervous system which he has inherited."[73] Once it has been demonstrated by painstaking effort that headaches are actually reduced in number and severity by such a philosophy, the patient is more likely to believe in it and thereupon to become more interested himself in making constructive observation and alteration of his own detrimental attitudes and habits of living.

At this point the question may be raised whether this form of migraine therapy lies in the province of the family physician, the specialist or the psychiatrist.

From both theoretical and practical considerations it appears that the family physician fills this role best for the majority of patients, provided he is interested in the problem and willing to devote the necessary time to it.[2] Certainly, the technics for helping patients to manage their lives in the presence of peptic ulcer, allergic disturbances, arthritis and a host of other common "office" problems are well known to him. The realization that the backbone of migraine therapy lies similarly within his grasp may encourage the family physician to undertake a positive approach to this problem more often and to be less prone to dismiss the patient with a packet of pills and the impression that "there is nothing that can be done about migraine." Certain patients in whom the family physician finds deep-rooted emotional problems to be playing a prominent part in the production of headache may be referred to a psychiatrist, with worthwhile results. Psychoanalysis has provided interesting information regarding the emotional dynamics of headache in some patients,[74] and in some hands has yielded significant relief. Frequently, however, such prolonged and expensive technics have failed to provide results commensurate with the undertaking.[75] A series of interviews at a more superficial level with a skilled psychiatrist appears to be more fruitful and practical for patients whose emotional problems exceed the scope of the family physician.

Short-Term Prophylaxis

Certain situations in the migraine patient's life are so commonly associated with the occurrence of attacks that special prophylactic measures seem indicated. Weddings, graduations, coming-out parties, christenings, reunions and other significant milestones in life's progress tend to produce a constellation of anticipation, anxiety and fatigue from excessive and tense preparation that presents the subject with a devastating headache just as the wonderful event takes place. Planned rest, mild sedation and the prophylactic use of ergot before and during such occasions can save the day. The use of Bellergal tablets, 1 before meals and 2 at bedtime, may be sufficient. An injection of Gynergen (0.5 cc.) or dihydroergotamine (1 cc.) at bedtime of the night before the event is perhaps the best insurance. Similar measures may be used for two or three days in a row to cover the changes of pace at the week end and the beginning and end of vacations. In these situations the patient may also be taught the value of "letting down" and "hitting the load again" in a gradual rather than abrupt fashion. The migrainous practice of working until midnight in a feverish endeavor to finish at the office and get everything packed for an early start frequently leaves the vacationer pain ridden and sick for the first two days of the precious holiday. Similarly, the benefits of the vacation can be quickly dissipated if the adjustment back to full activity is too precipitous. The same principles apply to the shorter interval of the week-end changes of pace. The avoidance of sleeping too late on Saturday and Sunday mornings, the planning of a schedule not too crowded with people and events and the use of a small amount of an ergot preparation on Friday, Saturday and Sunday nights are often effective prophylactic measures.

Migraine patients who have just been delivered or undergone a surgical operation often have an attack shortly after the event is over. Such headaches are occasionally attributed to the anesthesia or to a complication of the procedure, and the benefits of ergotamine are neglected. Victims of migraine do well to spend an extra day in the hospital before surgery and to remain somewhat longer after surgery or delivery than the usual modern "back-to-work" policy dictates.

The menstrual cycle is often associated with an increased frequency and severity of migraine. Various etiologic theories involving disturbed emotional, electrolyte, hormone and vascular balance have formed a basis for therapeutic recommendations.[76-78] The retention of salt and water in the premenstrual period in association with the development of headache has stimulated some investigators to recommend a program of sodium deprivation, and a low-carbohydrate and high-protein diet, with the administration of various diuretics such as ammonium chloride, Diamox and mercurials.[76,79] Such measures seem to influence some patients favorably but fail in many others. Closer analysis of this theory in recent studies by Ostfeld and his co-workers[80] suggests that the fluid and electrolyte retention at the time of the catamenia is not causally related to the menstrual headache. Other investigators, finding deficiencies of estrin and excesses of gonadotrophic-stimulating hormone in migraine patients at the time of their menstrual periods, have given estrogens in the week before menstruation or at various other times in the cycle, with variable results. Testosterone and progesterone given during the week before menstruation are occasionally useful.[18] The creation of an anovulatory cycle by the use of testosterone at the time of ovulation[82] or of large doses of estrogen beginning on the third or fourth day of the catamenia and continuing for twenty-five days is attended with success in a few patients. Unpleasant side effects of hormonal therapy of this type, such as irregularity of menstruation, menorrhagia and the occurrence of masculinizing signs and symptoms, are poorly tolerated by sensitive patients with migraine. Cortisone and ACTH, given in moderate doses to cover this headache-laden period, are also effective in some patients. The unpredictability of results and unpleasant side reactions of hormone therapy hamper its widespread use. In isolated cases it may be worth while, but, in the average patient, attention to lightening the schedule, provision for more rest and the prophylactic use of small amounts of sedation and ergot derivatives often

yield results that are as good or better in the long run. Potassium thiocyanate has proved surprisingly effective in preventing migraine in some patients.[83-85] Because of its toxic effects when used over long periods its popularity has declined. As interval therapy in doses of 100 mg. three times a day during the menstrual period, some of its disadvantages are avoided, and occasionally marked relief is obtained.

Various Prophylactic Agents

When the conscientious physician has done everything he can to strengthen his patient's general health, iron out the wrinkles of his living habits and fortify him with appropriate medication for his attacks, he may still be left with patients who continue to suffer from unpleasantly frequent episodes. Difficult life situations that defy solution and an extra large dose of the inherited migraine trait account for the majority of such patients. Friedman[81] has noted that "the family history in these cases reveals a preponderance of migraine in a ratio of 90 per cent in the refractory to 60 per cent in the nonrefractory group. . ." I have also noted that patients who have an inheritance of migraine from both sides of the family tend to run a more pernicious course. Whatever the reasons for such refractoriness may be, when the physician encounters it, he naturally gropes eagerly for some additional system of treatment that will help. Many such regimens have been suggested through the ages, ranging from the handkerchief knit about the brow, as suggested by Desdemona to Othello,[86] to being spun in the "human centrifuge."[87] The list is a long one and keeps changing kaleidoscopically. Promising regimens of a decade ago gradually lose their luster and fade out as new lights appear on the horizon. None have proved specific, few have been studied with proper controls, and yet many lend at times a much-needed hand. Those currently popular are recorded below. The details of their management are presented in the individual papers on each subject.

Histamine "desensitization." That histamine is a powerful dilator of human blood vessels has long been known. Clark, Hough and Wolff[88] demonstrated that the headache occurring in normal subjects after the intravenous administration of histamine is due to the resulting dilatation of cranial arteries. Horton et al.[89] found that patients suffering from a severe form of paroxysmal headache (subsequently termed by the authors "histaminic cephalgia") were peculiarly sensitive to histamine, small doses of which produced a characteristic and typical attack. Further studies suggested that this type of headache was related to migraine in its aberrant vascular physiology if not in its clinical picture. Treatment of such patients with increasing doses of histamine given either intravenously or subcutaneously seemed to bring relief. (Proper control studies are lacking, and there is much to suggest that the natural course of this remitting and exacerbating malady may account for many of the seemingly beneficial results.) The trial of this form of therapy in migraine was a natural outgrowth of the foregoing. Various workers have claimed a variety of results.[61,90-95] Its clinical use requires much of the juggling of dosages, repeated injections, special directions and even hospitalization involving enforced rest, all of which are such powerful therapeutic agents in themselves that it is difficult indeed to evaluate the isolated effect of the histamine. Application of the double-blindfold method of testing drug effectiveness would help to decide this issue. The possibility of activation of peptic ulcer, and even hemorrhage, during histamine therapy should be borne in mind.[92]

Histamine therapy has had two offshoots: neostigmine desensitization and antihistamine therapy. On the basis of the fact that acetylcholine has been thought to be the histaminelike substance in the body that may account for local vascular dilatation in patients with headache and because neostigmine by its power to inactivate cholinesterase, can be conceived of as capable of liberating acetylcholine, increasing doses of neostigmine bromide have been used to harden the body's defenses against this vasodilator.[96,97] Both the efficacy and the theory of this form of therapy remain in question.

Isolated cases of the effectiveness of the antihistamine drugs[98] make their consideration worth while in some patients. It has been my impression that they may prove more useful in the classic form of migraine than in "ordinary sick headache." Whether their effect, when present, is due to their antihistaminic properties or to their sedating qualities is undetermined.

Vitamin Products. Enthusiasm has risen, and in most cases fallen, for the use of many of the vitamin products as they have been synthesized. Especial attention has been given to thiamine hydrochloride[99] and riboflavin,[100] and more recently vitamin B_{12} has been used for a variety of head pains. Nicotinic acid occasionally seems to be effective in preventing classic migraine.[101] In general the vitamins may be thought of as harmless and possibly useful adjuncts to migraine therapy.

Sedatives. Barbiturates and other sedatives can rarely be claimed to have a specific effect on migraine but, as in other conditions in which neurogenic factors play an important part, often have a helpful influence. In patients who are found to have abnormal encephalograms and in whom the neurologic features of the attacks are prominent, the use of anticonvulsants, such as Dilantin,[102] is worth a trial. Whether the "tranquilizing" effects of the reserpine group of drugs will prove significantly useful in migraine remains to be seen. In some patients I have observed a favorable influence of a general sort, but

it does not appear that these agents hit migraine at its center.

Hormones. The short-term use of various hormones for menstrual migraine has been treated already. More prolonged regimens have also been advised. Whenever they are used, the physician should make a point of seeing the patient frequently enough to be sure that deleterious side effects are not developing.

Prolonged treatment with large doses of estrogens frequently has a suppressive effect on migraine in women. Eventually, "escape" usually occurs. Swollen, painful breasts, metrorrhagia and menorrhagia are apt to occur and at times create worse difficulties than migraine. Blumenthal and Fuchs[103] and others have found a repetitive system of using estrogen for twenty days followed by progesterone for ten days to be well tolerated and definitely beneficial in certain patients. Androgenic therapy, as recommended by Moehlig and Gerisch,[104] brings relief to some women and some men, but is not well tolerated for long, since the occurrence of acne, hirsutism, voice changes, menstrual irregularity and altered libido are frequent unless the doses are kept low and treatment is periodically interrupted. Both androgens and estrogens seem to have a nonspecific effect of increasing the stamina of the tired, delicate migraine victim during the menstruating years. When used separately or in combination during the menopause, they may be definitely beneficial, especially in patients who exhibit an exacerbation (or even the onset) of migraine at this time in association with a multitude of "hot flashes."

Moffatt[105] and, more recently, Leyton[106,107] have advised the use of gonadotrophic-stimulating hormone in migraine. I have not found it as useful as these reports indicate. Many migraine patients have low basal metabolic rates (−20 to −30 per cent), usually without clinical stigmas of or blood iodine levels consistent with true hypothyroidism. In such patients the use of desiccated thyroid has been reported to be beneficial to the migraine.[108] That this is not a specific effect is illustrated by the course of 2 patients observed at the Massachusetts General Hospital, 1 of whom had a severe exacerbation and the other a remission of her migraine when true hypothyroidism was created by radioactive iodine. Cortisone and ACTH possess a dramatic capacity to suppress migraine.[67,109] Unfortunately, as in other chronic diseases similarly affected by steroids, symptoms regularly recur after withdrawal of the drugs, and the amounts necessary to obtain relief create side effects and dangers that preclude their long-term administration. Their place in the treatment of the acute attack and as interval therapy at the time of menstruation has been discussed. In certain desperate situations of "migraine status" (as described below) their use may be justified.

Dietotherapy. Many observations have been made through the ages on the influence of diet on migraine. The importance of its quantity as well as its quality was stressed in 1784 by Sir John Fothergill.[110] Allergenic properties of the diet and the use of elimination diets have been stressed by more recent authors.[61,111-113] The headache-producing effects of carbohydrate,[114] protein[115] and fat[110] have received attention, and the therapeutic value of the ketogenic diet, borrowed from the therapy of epilepsy, has been suggested.[116,117] The variety of these recommendations suggests that the discipline of following the given regimen rather than its nature is important. Some migraine patients have found through hard experience that certain foods produce headache. For them, the elimination of these offenders seems only reasonable. The more complicated regimens are hard to follow and frequently forsaken and sometimes become an obsession. In allergic children, attention to the diet seems more rewarding than in adults. Perhaps the best over-all recommendation is that for migraine patients the diet should be well balanced and eaten on time and under peaceful, pleasant circumstances.

Other measures. Bile salts,[118] potassium thiocyanate,[83-85] sympatholytics such as Hydergine,[2] Octinmucate,[2] calcium lactate and potassium chloride mixtures,[121] amphetamine compounds,[2] oxygen inhalation[65] and neck traction and physiotherapy[2] have all had their advocates. None have proved universally effective, and many, after a period of popularity, seem to have been abandoned.

Surgical Relief

Certain patients with migraine that is recurrently localized in one area of the head who have found no relief from medical measures may be considered candidates for a variety of surgical procedures that have offered variable degrees of success. Removal of various organs remote from the head, such as the appendix, gall bladder, uterus and ovaries, is contraindicated. Creation of an artificial menopause by surgery or irradiation should be discouraged, since the chances of making the migrainous condition worse are greater than those for improvement.[6,122,123]

Although a few dramatically successful examples of surgical relief may be cited, relief by these means is more frequently apt to be temporary, attended by the eventual recurrence of the migraine in another area or followed by some unpleasant complication of the operation that may be poorly tolerated, such as Horner's syndrome, failure of lacrimation and keratitis, or unpleasant paresthesias. Such sequelae may be overbalanced by the relief obtained, but should be kept in mind when surgical therapy is evaluated. These operations may be divided into the following groups: subtemporal decompression[124]; interference with autonomic fibers in the neck,[125,126] carotid sheath[127] or greater superficial petrosal nerve[128]; ligation of the external carotid artery or its branches[129];

infiltration of superficial arteries, cervical nerves or the gasserian ganglion with procaine or alcohol[130,131]; surgical interruption of cervical roots or nerves[132]; and surgical interruption of the sensory pathways of the fifth nerve in the form of either postganglionic neurectomy or medullary tractotomy.[133,134] All these measures should be preceded, if possible, by preliminary procaine infiltration of the proposed site of operation during a *severe* attack. Failure to get relief when the physiologic defect has been reproduced by novocain augurs failure by surgery. Unfortunately, novocain success does not always promise surgical relief. Of these procedures, subtemporal decompression and autonomic surgery seem gradually to have lost favor. Novocain and alcohol infiltration of nerves and arteries tends to bring temporary benefits. Ligation of arteries and their sheaths and section of sensory tracts offer more promise. Occasionally, the operation involving ligation of the temporal artery and avulsion of the auriculotemporal nerve brings striking relief and can be recommended without misgivings because of its simplicity and lack of unpleasant sequelae. By and large, the migraine surgeon may be compared with the gardener who cuts off the tops of the weeds rather than pull them up by the roots. Sometimes, the noxious plants grow again in their original site, and at other times they sprout up with renewed vigor in new locations. Surgery for migraine can be a useful ally in a difficult situation but should be reserved for selected patients in whom other measures have failed, and then placed in the hands of a conservative and experienced neurosurgeon.

Migraine Status

Fortunately, this state is attained by only a few patients. When it occurs, plans should be made for a long and difficult siege. Hospitalization of the patient is almost a *sine qua non*. A firm confidence in the doctor must be gained before the necessary removal of excessive amounts of drugs, especially ergot derivatives, barbiturates and narcotics, can be effected. A month in the hospital is frequently required, followed by another month or two at home or in a rest home, free from work, care and responsibility. Patient, family and employer should understand the importance of sufficient time for recovery. Quiet, good food, attention to every aspect of the patient's physical disabilities and, eventually, occupational therapy and graduated exercise are necessary. Formal psychotherapy at this stage is not as effective as firm and friendly support. The use of vitamins and insulin to stimulate appetite is helpful. Chlorpromazine may be of value during the period in which other drugs are being reduced. Headache frequently does not begin to let up until two weeks of such a program have been in operation. In recalcitrant cases the use of small amounts of steroids, preferably for a period not exceeding three weeks, may be justified and helpful. Re-education and suitable alteration of plans for the future should be undertaken before the patient is permitted normal activity, or the good work will be undone.

Conclusions

The treatment of migraine is difficult but worth the effort. It tops every resource of the physician for its success. Probably more hours of suffering are caused by it than any other human affliction. Knowledge of its secrets is incomplete but increasing. For these reasons it presents a unique challenge.

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MEDICAL INTELLIGENCE

GROWTH OF FORTY-THREE ALLERGIC CHILDREN DURING CORTISONE ADMINISTRATION

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WHEN I began to treat certain allergic children with cortisone, Dr. Nathan B. Talbot, of the Massachusetts General Hospital, told me that this hormone might retard their growth. Table 1 shows the growth of 43 such children (32 with asthma and 11 with eczema) six months to twelve years of age. The duration of treatment varied between three and thirty months; 15 patients were treated for more than twelve months. No child was given over 75 mg. of cortisone a day; only 1 received as much as this for longer than ten days. The usual maintenance dose varied between 25 and 50 mg. a day. In all children cortisone treatment was continuous and given by mouth.

Twenty-four children gained in height below the average rate, 15 above the average, and 4 the same as the average. In 417 months of cortisone treatment 43 children grew in the aggregate 80.75 inches. The average gain in the same number of months for 43 normal children of the same sex, age and percentile height group, according to the tables, would be 86.20 inches, a deficit of about 7 per cent for the cortisone-treated children. Nine of the 24 children who grew at less than the average rate had a deficit of only 0.25 inch for periods varying from three to thirty months. Of the 15 children who took cortisone for a year or more (Cases 29-43), 5 grew at the average rate or above it, and 10 less than the average rate; in 3 of these 10 the deficit was only 0.25 inch, which is negligible. In Cases 30, 33, 35 and 38 the deficit was enough to be of possible importance.

DISCUSSION

It is by no means a simple matter to determine whether a group of children who are taking cortisone grow at a slower than average rate, because it is not known at what rate these children were growing before they began to take cortisone or after they stopped taking it, because there is a seasonal variation in the growth of children, and because there can normally be a great variation from the average growth curves.

This work was reviewed by Dr. Harold Stuart, of the Harvard School of Public Health, and by Dr. Robert Reed and Miss Elizabeth Grant, associated statisticians. They agreed that "the figures provide no satisfactory evidence that there is a real difference between these cortisone-treated children and normal children in respect to rate of growth. It is also obvious that the data are not sufficient to conclude that such a difference does not occur."

TABLE 1. *Growth of 43 Children Taking Cortisone.*

Case No.	Age	Duration of Treatment	Gain in Height	Average Normal Gain*	Height Gain Below Average	Height Gain Above Average
		mo.	in.	in.	in.	in.
1	9 yr.	3	0.75	0.50		0.25
2	22 mo.	4	1.00	1.00	0.00	0.00
3	2½ yr.	5	0.75	1.25	0.50	
4	2 yr.	8	1.75	2.00	0.25	
5	6 yr.	6	1.50	1.25		0.25
6	6½ yr.	3	1.50	0.50		1.01
7	12½ yr.	6	1.25	1.00		0.25
8	5 yr.	4	1.25	0.75		0.50
9	7 yr.	11	1.50	1.75	0.25	
10	6 mo.	3	1.50	2.00	0.50	
11	9 yr.	3	0.25	0.50	0.25	
12	10 yr.	4	1.25	0.75		0.50
13	4 yr.	7	1.75	1.25		0.50
14	5½ yr.	4	1.00	0.75		0.25
15	27 mo.	3	0.25	1.00	0.75	
16	12 yr.	5	1.00	1.00	0.00	0.00
17	3 yr.	4	0.75	1.00	0.25	
18	8 yr.	4	1.00	0.50		0.50
19	2 yr.	9	2.00	2.00	0.00	0.00
20	4 yr.	6	1.00	1.50	0.50	
21	9 yr.	3	0.75	0.50		0.25
22	11 yr.	3	0.50	0.75	0.25	
23	3 yr.	5	1.00	1.50	0.50	
24	22 mo.	7	1.00	1.75	0.75	
25	2 yr.	3	1.25	1.00		0.25
26	3½ yr.	3	0.50	1.00	0.50	
27	8 yr.	9	2.00	1.75		0.25
28	7 yr.	8	1.50	1.75	0.25	
29	6 yr.	14	2.50	3.25	0.75	
30	7 yr.	18	2.00	3.75	1.75	
31	7 yr.	12	2.25	2.25	0.00	0.00
32	6 yr.	19	3.50	4.25	0.75	
33	4 yr.	20	3.75	4.75	1.00	
34	3½ yr.	14	2.75	3.00	0.25	
35	8 yr.	20	2.50	3.75	1.25	
36	7 yr.	24	4.50	4.00	0.50	
37	9 yr.	19	3.25	3.00		0.25
38	4½ yr.	12	2.75	2.25		0.50
39	4½ yr.	26	4.75	5.75	1.00	
40	12 yr.	16	3.00	2.25		0.75
41	8 yr.	18	2.75	3.50	0.75	
42	10 yr.	14	1.75	2.00	0.25	
43	5 yr.	30	6.00	6.25	0.25	

*From Stuart, H. C., and Stevenson, S. S. Physical growth and development. In *Mitchell-Nelson Textbook of Pediatrics.* Fifth edition. 1658 pp. Edited by W. E. Nelson. Philadelphia: Saunders, 1950. Pp. 60-70.

Conclusions

The only conclusion that can be drawn from these observations is that if there is any retardation of growth in allergic children who are taking moderate or small amounts of cortisone, the retardation is not great and is not sufficient to warrant withholding cortisone when it is needed.

From a practical point of view this fact is what one wants to know when cortisone treatment is indicated in children.

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VALSALVA'S MANEUVER AND WEBER'S EXPERIMENT*

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NEW ORLEANS, LOUISIANA

FORCEFUL expiration against the closed glottis is commonly known as the "Valsalva experiment."

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The detailed report of Weber contrasts with the absence of documentation linking Valsalva with the experiment. We therefore consider the eponym not entirely suitable.

Valsalva[1] described a maneuver useful in expelling pus from the middle ear. It consisted of expiring against the closed nose and mouth. No observations of the circulatory effects were mentioned. Valsalva's original statement and our translation are as follows:

> . . . si, inquam, iste clauso ore et naribus aerem intro comprimere conetur; inde sanies in meatum auditorium ita copiose solet eodem actu protrudi, ut ad istiusmodi ulceris detersionem nullum promptius, aut utilius ægris remedium commendare consueverim; quam mediocriter frequentem talis conatis iterationem.
>
> . . . if, I say, he should attempt to compress the air within, after having closed his mouth and nostrils; the exudate usually is pushed forth thereby copiously into the auditory meatus; so that I am accustomed to recommend nothing more rapid in cleansing an ulcer of this kind, or remedy more useful for the patient than a fairly frequent repetition of such an effort.

Edward Weber,[2] of Germany, one of three brothers famous in physiology, reported in clear detail the effects of forced expiration against his closed glottis in 1851. He ascribed the effects to compression of the thorax and, not as previous writers had held, to breath holding per se. Our translation of Weber's description follows:

> Several years ago I found through experiments on myself, which I showed my scientific friends, that I can

voluntarily act in such a way that the heart and pulse beat almost immediately disappear when I close the exit of air from the chest and simultaneously compress the chest . . .

Just as with the heart beat, all the sounds associated with movements of the heart disappear immediately: one may seek with the stethescope or the ear applied directly to the chest for the sounds of the auricles, the ventricles, the tone of the aorta as well as that of the pulmonary artery; on the other hand one still feels 3 to 5 very weak pulse beats. The pulse then stops with a definite beat and does not become gradually imperceptible . . .

The reported experiments permit no doubt; the result is so certain that I am not only able to demonstrate the phenomenon, but anyone can do this if he knows the manner of bringing it about. The fact as described here is equally unknown. There is no mention of it in the larger works on physiology and the special writings concerning the heart and circulation . . .

Dawson[3] stated that Weber had overlooked Valsalva's observation. Dawson cited Luciani[4] and said the observation was found in letter 19 of Morgagni's[5] *De sedibus.* Morgagni was Valsalva's principal pupil, and many consider their contributions joint efforts. Luciani quoted neither Morgagni nor Valsalva and gave references to neither, but placed Valsalva's name in parentheses after describing the experiment. This description is placed in quotation marks in Dawson's article. Neither in letter 19 nor in the other works of Morgagni is this or a similar statement to be found.

In letter 19, Article 33, the effect of respiration on neck veins in dogs was noted:

Valsalva, therefore, having cut open the skin in the neck, and laid bare the jugular veins, observed that these vessels, which were turgid with blood, became less tumid, when the dog inspired; but in expiration, that they again became turgid, especially when the respiration approached more nearly to its natural state . . . as far as I know, had been seen by no body till that time besides Valsalva . . .

In discussing the cause of death by hanging Morgagni offered the following observation in Article 38 of letter 19:

But I do not now say, that no blood passes through the lungs, immediately on respiration being impeded; but that it passes in less quantity, and after that in less, and less, so that what does pass, cannot be sufficient to preserve the circulation: . . . but in the meanwhile, the right ventricle of the heart is so dilated with blood that it cannot presently constringe itself, nor drive on even a small quantity of blood, through the lungs, to the left ventricle, and the arteries.

We found, however, no statement about forced expiration and its effect in man. Dawson and Luciani could not have referred to Morgagni's[6] major work on Valsalva, which contained only 18 letters.

In 1869 Longet[7] mentioned Valsalva's and Morgagni's observations of venous flow and respiration and correctly cited Morgagni's letter 19. In 1880 Hermann[8] defined the Valsalva experiment as it is termed today, but cited no references.

Wird aber die Ausathmung oder die Einathmung forcirt, oder wird sie z. B. durch Verschluss eines Nasenloches behindert, oder wird nach kräftig ausgeathmet (Valsalva's Versuch), oder nach vorausgehender Expiration eben so eingeathmet (Müller Versuch*) . . .

If, however, expiration or inspiration is forced, or if hindered for example by closure of the nostrils, or afterward strongly exhaled (Valsalva's experiment), or after previous expiration similarly inhaled (Müller's experiment) . . .

Experiment is defined[9] as "a procedure gone through in order to discover or to demonstrate some fact or general truth." "Any dextrous proceeding" is considered a *maneuver.*[9] It seems appropriate to honor Valsalva's contribution by using his name when the act is used as a therapeutic maneuver. In the otolaryngeal literature the term is employed in this stricter sense. If the word "experiment" is applied to the act of forceful expiration against the glottis it seems proper to designate this "Weber's experiment"

*Perhaps an erudite physiologist could cite the origin of this term. It has, so far, eluded us. Dawson's reference gives but meager substantiation, and no clear statement is found in Müller's text.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41451

PRESENTATION OF CASE

First admission. A fifty-three-year-old male physician entered the hospital complaining of substernal tension.

For two months the patient was aware of substernal tension relieved by lying down. This sensation was not definitely related to exertion and did not radiate into the arms or neck. He had been overworking and was smoking 1 or 2 packages of cigarettes daily.

Physical examination was negative. The pulse was 80, and the blood pressure 134 systolic, 90 diastolic.

Examination of the blood cells was negative. The blood sugar was 89 mg., and the nonprotein nitrogen 33 mg. per 100 cc. A phenolsulfonphthalein test showed 25 per cent excretion in fifteen minutes and 55 per cent in two hours. A blood Hinton test was negative. An electrocardiogram showed normal rhythm at a rate of 80 to 85, with low upright T waves in Lead 1. An x-ray film of the chest demonstrated slight tortuosity of the aorta but was otherwise normal.

On completion of these studies the patient was advised to cut down on his smoking and to take a vacation.

Second admission (nine years later). He was well until nine days before entry, when he noted the onset of steady, severe, sharp pain in the left flank. A retrograde pyelogram showed left-sided hydroureter and hydronephrosis. The pain continued to the time of admission.

Physical examination was negative except for slight tenderness in the left costovertebral angle, and a Grade 1, apical, systolic murmur at the cardiac apex. The aortic second sound was greater than the pulmonic.

The temperature was 97.8°F., the pulse 100, and the respirations 20. The blood pressure was 150 systolic, 85 diastolic.

The urine had a specific gravity of 1.014 and gave a ++ test for albumin: its sediment contained 4 red cells per high-power field and was loaded with white cells. Examination of the blood revealed a hemoglobin of 13.4 gm. per 100 cc. and a white-cell count of 16,500, with 87 per cent neutrophils. The nonprotein nitrogen was 47 mg. per 100 cc. Urine culture grew *Escherichia coli.* An electrocardiogram showed no significant change from the previous tracing. X-ray films of the chest revealed considerable tortuosity of the aorta. There was a suggestion of nodularity of the descending thoracic aorta, which raised the question of dissection. A retrograde pyelogram suggested a hollow structure in or near the expected location of the left lower ureter. Cystoscopic examination showed the left ureteral orifice to be quite small. No urine was obtained from this side.

The patient underwent a left thoracoabdominal nephrectomy and ureterectomy, and the pathological report was chronic pyelonephritis, hydronephrosis and hydroureter. He was discharged on the seventeenth postoperative day.

Third admission (fourteen months later). He was well except for a mild chronic cough until two weeks before admission, when he coughed and expectorated a mouthful of bright-red blood. He then continued to expectorate blood-streaked sputum every day or every other day. He was still smoking 1 or 2 packages of cigarettes a day. There was no chest pain, wheezing, weight loss or shortness of breath. He had noted a rise in blood pressure since the nephrectomy.

Physical examination revealed decreased breath sounds in both upper-lung fields and a few coarse rales throughout both lung fields. The heart showed minimal enlargement and a Grade 2, apical, systolic murmur. Examination of the nose, throat and larynx was negative.

The pulse was 78, and the respirations 20. The blood pressure was 175 systolic, 105 diastolic.

Urinalysis showed a specific gravity of 1.026 and 3 white cells per high-power field in the sediment. Examination of the blood revealed a red-cell count of 4,000,000 and a white-cell count of 12,500, with a normal differential. The blood sedimentation rate was 24 mm. in one hour. The nonprotein nitrogen was 43 mg. per 100 cc. The phenolsulfonphthalein excretion was 64 per cent in two hours. Sputum smears and guinea-pig inoculations were negative for acid-fast bacilli. An electrocardiogram showed normal axis, upright T waves in Leads 1, 2, 3, aVF, V_1, V_2, V_3, V_4 and V_5, low diphasic T waves in Lead aVL, and low upright T waves in Lead V_6. An x-ray film of the chest showed greater prominence of the aorta in its descending thoracic portion (Fig. 1). This again was suggestive of dissection. The heart shadow was increased slightly in size since examination two years previously. The lungs appeared clear.

Bronchoscopy gave no evidence of bleeding from the bronchial tree. The patient was discharged after four days in the hospital.

Final admission (two and a half months later). In the interim he was well, except for coughing up a blood clot on one occasion. Two nights before entry he noted the onset of mild epigastric distress. The next morning while he was at work pain appeared in the low midback and increased in severity. A physician found the blood pressure to be 270 systolic, 130 diastolic, and administered morphine. Within a few hours the blood pressure fell to 60 systolic, 40 diastolic, and the patient was in a cold perspiration and had a rapid pulse. He vomited already digested food. There was no loss of consciousness or increase in pain at this time. An electrocardiogram was said to be "negative." The white-cell count was 30,000. The serum amylase was negative. Cedilanid was administered. During the night before admission physical examination revealed distant but regular heart sounds. There was an apical systolic murmur unchanged from previous examinations. The lungs were clear. The pulse was 112. The blood pressure was 136 systolic, 80 diastolic, in both arms, and all

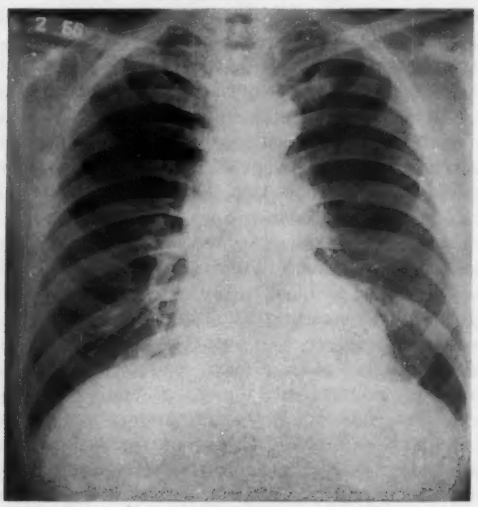

FIGURE 1. *Examination of the Chest, Showing Moderate Tortuosity of the Aorta and Some Prominence of the Left Ventricle.*

pulses were palpable. He was admitted to the hospital on the next day.

Physical examination revealed a lethargic, pale, elderly man in no acute distress, but somewhat agitated when aroused. There was dullness, tubular breathing and decreased tactile fremitus, but no rales over the left-lower-posterior-lung field. There was a loud, Grade 4, aortic, systolic murmur radiating to the neck and to the apex. The pulses were full.

The temperature was 98°F., the pulse 100, and the respirations 16. The blood pressure was 160 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 9.7 gm. per 100 cc. and a white-cell count of 28,900. The nonprotein nitrogen was 96 mg. per 100 cc. The prothrombin time was 14 seconds (70 per cent of normal). An electrocardiogram showed sinus tachycardia at a rate of 110, a PR interval of 0.16

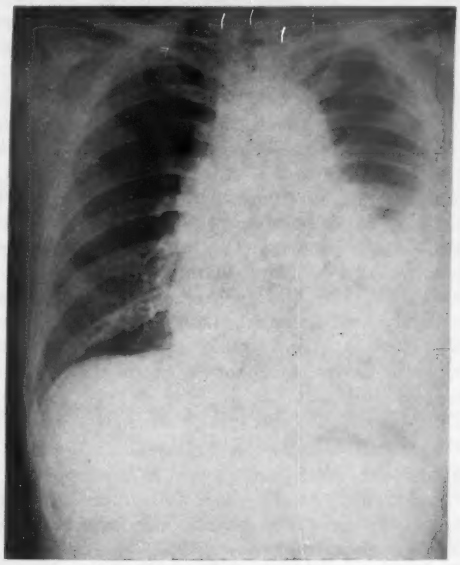

FIGURE 2. *Examination of the Chest, Showing the Widening of the Mediastinum Thought to Result from a Dilated Aorta and Left-Sided Pleural Effusion.*

second and a QRS interval of 0.08 second. The ST segments were slightly sagging in Leads 1 and V_4 through V_6, and the T waves were inverted in Leads 1, 2, aVL, aVF and V_4 through V_6. Fluoroscopy showed the left heart border to be obscured by fluid in the left pleural space. The aorta was more prominent both to the left and to the right of the midline. The descending thoracic aorta at the level of the sixth intercostal space appeared to swing more laterally, which was also suggestive of increase in the size of the aorta (Fig. 2). Thoracentesis was productive of 5 to 10 cc. of grossly bloody fluid. On the second hospital day the patient was noted to be somewhat hoarse. The blood pressure remained at about 170 systolic, 100 diastolic. During the entire hospital course there was no urine output. On the third day the nonprotein nitrogen was 96 mg. per 100 cc., and the patient became clinically uremic, showed a Kussmaul type of breathing and died.

DIFFERENTIAL DIAGNOSIS

DR. GORDON S. MYERS*: May I see the last electrocardiogram? This tracing shows nonspecific ST-

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segment and T-wave changes in Leads 1, 2, aVL and aVF and in the left chest leads. These may in part be due to digitalis effect. In any event, there is no diagnostic evidence of myocardial infarction.

Dr. Wang, perhaps we should look at the x-ray films now.

DR. C. C. WANG: The films of the chest taken approximately two and a half years before the last admission show the lung fields to be clear. The heart is not unusual in size, and the aorta is somewhat tortuous. Approximately two years later the films show that the cardiac shadow is somewhat larger, and the aorta is more tortuous than previously (Fig. 1).

DR. MYERS: Do you see any calcification within the aorta?

DR. WANG: None of which I can be sure. The chest films taken on the last admission demonstrate a greatly dilated aorta; the transverse diameter of the aortic knob certainly is much larger than previously (Fig. 2). The ascending aorta also is more prominent than usual, protruding into the right lung field. There is a considerable amount of fluid in the left pleural cavity. I cannot be sure of the outline of the descending aorta.

DR. MYERS: Do you think that there is any fluid in the pericardial sac?

DR. WANG: Yes; there could be.

DR. MYERS: At the time of the third admission when the patient was having hemoptysis, did the lungs look abnormal?

DR. WANG: I do not see any disease in the lungs to account for the hemoptysis.

DR. MYERS: I think I can safely hurry over the first two admissions, although to do so is always risky under these circumstances. At the time of the first admission the symptoms, mainly a sensation of discomfort in the chest disappearing with recumbency, were poorly defined. Studies in the hospital were within normal limits, and, so far as I can judge from the protocol, the symptoms disappeared after reassurance. I do not believe that this episode had anything to do with the final difficulty, but it did provide a useful base line.

The second admission is also difficult to tie in with the final illness of this patient. He had symptoms, signs and also pathological findings that were consistent with chronic pyelonephritis, hydronephrosis and hydroureter on the left side. However, we are not given any information about the cause of the obstruction to the ureter. I suppose it could have been due to the passage of a stone at a previous time or to inflammatory changes. The x-ray film suggested possible dissection of the aorta so that we must consider whether a dissection of the aorta could have given rise to the renal disease. Dissecting aneurysm, by involvement of the renal arteries, can cause infarction of the kidneys and result in hematuria or anuria. One case has been reported in which a large retroperitoneal hemorrhage involved the kidney and ureter. In view of the fact that this patient's chest and abdomen were explored surgically and that a pathological specimen was obtained, I cannot believe that a dissecting aneurysm was responsible for this episode, and I am inclined to take it at face value.

The third admission was occasioned by painless hemoptysis of two weeks' duration. The only striking change at the time was a considerable increase in blood pressure — apparently present since the left kidney had been removed. There was slight anemia and leukocytosis, but no fever. Bronchoscopy and x-ray films of the chest showed no lesions within the lung, but once more there was some question of dissection of the thoracic aorta. Dissecting aneurysms can cause hemoptysis, although this does not occur often. In the cases that I have read about in which hemoptyses occurred, there has been a dissection along the pulmonary arteries and into one or both lung roots. Certainly, if this patient had hemoptysis on the basis of a dissection, one would have expected him to have pain, but sometimes pain is mild or absent. In a patient surviving for this period, in addition to the leukocytosis there should also have been fever. It is possible that there was a dissecting aneurysm and that there had been a very tiny leak of blood into the bronchial tree that was not picked up by bronchoscopy because the bleeding had ceased. However, it is well known that in some patients with gross hemoptysis, careful study will fail to demonstrate the source of bleeding; there need be no serious underlying cause. In view of the eventual outcome, I am inclined to believe that this patient's hemoptysis was related to a dissecting aneurysm.

The final admission, two and a half months later, was for epigastric pain that later radiated to the lower back. The blood pressure was initially very high and after narcotic administration fell to shock levels. That sequence of events — pain followed by greatly elevated blood pressure and then shock — is certainly consistent with dissecting aneurysm, as are the initially normal electrocardiogram, the elevation of the white-cell count, the aortic systolic murmur, the evidence of bleeding into the left pleural cavity, the x-ray picture of considerable widening of the thoracic aorta and the anuria. The diagnosis of dissecting aneurysm is not invalidated by failure to demonstrate unequal or absent pulsations in the major arteries, since this is demonstrated in a minority of cases.

The pain of dissecting aneurysm is characteristically very severe at onset; it often radiates to the back, usually beginning in the chest or epigastrium. Elevation of the blood pressure during the initial attack probably often results from accentuation by pain of a pre-existing hypertension; it may also be accounted for by partial obstruction to the aorta occasioned by ballooning out of the intima. Later, of course, very low blood pressures may appear as a result of rupture

and hemorrhage. The electrocardiogram is usually abnormal, often showing the picture of hypertensive heart disease. Nonspecific ST-segment and T-wave changes consistent with coronary insufficiency may also appear, especially in patients in the older age group during a period when there is a considerable fall in blood pressure. Cases of myocardial infarction without actual occlusion of the coronary arteries have been reported under these circumstances. Myocardial infarction rarely occurs as a result of involvement of the coronary arteries in the dissection. Sometimes the electrocardiograms will show changes indicative of pericarditis, secondary to a myocardial infarction, to uremia or rarely to a slow leakage of blood into the pericardial sac. The last electrocardiogram in this case, I think, falls in the category of the so-called ischemic pattern, without definite evidence of myocardial infarction and without being characteristic of pericarditis.

Patients with dissecting aneurysm who survive long enough nearly always show leukocytosis and fever unless they are in shock. This patient's anemia can easily be explained by the fact that he bled into the left pleural cavity and may have bled elsewhere. In many patients aortic diastolic murmurs develop, presumably because of distortion of the aortic valves by the dissection, but in an equal number the aortic systolic murmurs perhaps result from the turbulence of blood as it passes the dissected intima just above the aortic valve.

Terminally, this patient became anuric. There is no information about the amount of urine passed before he entered the hospital. The anuria may have been caused by involvement of the renal artery by the dissecting process. Persistent shock may have been sufficient to cause cessation of renal function also.

I cannot explain this whole picture satisfactorily by any other diagnosis so I am ready "to swallow" the suggestion of dissecting aneurysm given in the protocol. I believe that this patient had a dissecting aneurysm probably originating in the ascending aorta, not far above the aortic cusp, with rupture into the left pleural cavity, dissection along the pulmonary arteries and involvement of the right renal artery producing infarction of the right kidney. Some bleeding into the pericardium may have occurred, since it commonly does, but there was no clear evidence of it. I should expect that the heart was enlarged, with signs of hypertensive heart disease. There may have been some coronary-artery disease as well, but there was no proof of myocardial infarction or involvement of the coronary arteries.

Dr. Winfield S. Morgan: Does anyone want to suggest any diagnosis other than a dissecting aneurysm?

Dr. Warren Point: Does Dr. Myers think that the red-cell count of 4,000,000 two and a half months before death was significant?

Dr. Myers: It may have been. I think it is impossible to determine why the hemoptysis occurred, but I suspect that there was dissection along the pulmonary arteries and into the lung root at that time.

Dr. Jacob Lerman: I should like to ask Dr. Myers if it is a little unusual to have dissection down as far as the kidneys without diminution of the peripheral pulses in the arms.

Dr. Myers: In the reported cases, proved at autopsy, the observation of absence or inequality of peripheral pulses was made in a minority of the patients, even when the dissection was extensive.

Dr. Lerman: It is stated that the pulses were full.

A Physician: I should like to ask Dr. Myers when he thinks the dissection first began.

Dr. Myers: I think that it is within the realm of possibility that the symptoms on the first admission had something to do with a slight dissection of the aorta, but that the dissection probably first occurred on the third admission.

Clinical Diagnosis

Dissecting aneurysm of aorta.

Dr. Gordon S. Myers's Diagnoses

Dissecting aneurysm of ascending aorta, with involvement of right renal artery and rupture into left pleural cavity.
Hypertensive heart disease.

Anatomical Diagnoses

Dissecting aneurysm of descending thoracic aorta, with rupture into mediastinum and left pleural cavity.
Aortic atherosclerosis, with occlusion of right renal artery and renal infarction.
Slight aneurysm formation, thoracic.
Coronary sclerosis.
Cardiac hypertrophy, hypertensive type (weight, 490 gm.).

Pathological Discussion

Dr. Morgan: I do not think that we can explain the hemoptysis on the third admission, nor am I sure that we can relate the two earlier admissions to the final one. The patient had, as Dr. Myers predicted, a dissecting aneurysm, but this certainly was unusual. There was considerable atherosclerosis of the aorta, which was moderate from the root of the aorta to just beyond the great vessels, relatively slight in the next 7 to 10 cm., and then very severe with large plaques throughout the remainder of the aorta. The dissection occupied only the slightly involved portion beginning just beyond the great vessels and stopping just proximal to the severe arteriosclerotic changes. A very careful search was made of the intima and especially the ulcerated atherosclerotic

plaques, but no intimal communication with the dissection channel could be found. There was, however, a rent in the adventitia through which the blood had poured into the left pleural cavity, some 2000 cc. being found there. There was also dissection around the esophagus and into the mediastinum and the root of the lung.

DR. MYERS: Do you think that that may have accounted for the hemoptysis even though you could not find a point of entry into the bronchial tree?

DR. MORGAN: What was the interval there — two and a half months?

DR. MYERS: Yes.

DR. MORGAN: I do not know how we can answer that.

The heart weighed 490 gm. and gave evidence of hypertensive cardiomegaly, the left ventricle measuring 19 mm.

In the cortex of the remaining kidney, there were several pale areas of recent infarction, the largest measuring about 1 cm. The renal artery near the kidney was wide open, but at its junction with the aorta it was so narrowed that a 1-mm. probe could not be introduced into it. There was a small bit of fibrin there too. This was not total infarction of the kidney, and I am not sure we can explain the anuria over a period of three days except possibly on the basis of shock.

DR. MYERS: Was the dissection of the aorta responsible for the narrowing of the renal artery, or was that purely arteriosclerotic change?

DR. MORGAN: The narrowing was due to arteriosclerosis at the origin of the renal artery. The distal portion of the dissection was some distance above it. Our histologic sections through the region of dissection showed preservation of the elastica and loss of the muscle elements only focally. The vasa vasorum in the media were very numerous and dilated, and were surrounded by chronic inflammatory cells. The dissection was confined to the media except where it had ruptured through the adventitia. Gore and Seiwert,[1] in a study of dissecting aneurysm, found that 63 per cent of dissections began in the ascending aorta just above the aortic valve, 18 per cent at the transverse aortic arch, and 10 per cent in the distal aortic arch. The location of the hemorrhage in these cases is of particular interest. In all but 2 in that series of 69 cases the hemorrhage occurred above the diaphragm — 52 into the pericardium, 14 into the mediastinum, and 18 into the pleural cavities.

The etiology of dissecting aneurysm still is not definite, but the current view is that weakening of the vasa vasorum in the aorta as a result of medial degeneration, plays an important role — that probably under certain circumstances these vessels rupture, leading to hemorrhage and dissection into the media. This idea has been given considerable support by the pathological changes noted in the vasa vasorum and the fact that a significant number of cases of dissecting aneurysm have been reported[2] in which no intimal tear or communication between the aortic lumen and the dissection channel has been found.

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CASE 41452

PRESENTATION OF CASE

First admission. A sixty-two-year-old Lithuanian-born painter was admitted to the hospital because of pain in the right upper quadrant of the abdomen.

Ten months before entry the patient began to pass watery stools, which contained bright-red blood; after a few months he became constipated, but the melena continued. Three days before admission marked the onset of pain in the right upper quadrant of the abdomen radiating to the right shoulder posteriorly and made worse by moving, breathing and coughing. An x-ray film of the chest revealed slight elevation of the right leaf of the diaphragm and limitation of its motion because of adhesions to the lateral wall of the chest. A barium-enema examination demonstrated an annular lesion of the rectosigmoid. An adenocarcinoma, Grade 2, of the sigmoid, with metastases to 4 of 30 lymph nodes, was resected. No liver metastases were noted. The carcinoma invaded the serosa and surrounding fat and was 5 and 11 cm. from the proximal and distal resection edges respectively. Three small mucosal polyps were also present in the resected specimen.

Second admission (six years later). After discharge the patient complained intermittently of headaches and constipation. However, x-ray studies of the chest, barium-enema procedures and physical examinations were repeatedly negative until nine months before admission, when, on a routine outpatient examination, the liver was noted to be enlarged 4 cm. below the costal margin. At this time the patient was complaining only of gaseousness. Two months later he experienced the sudden onset of pain in the right upper quadrant of the abdomen and the right flank, with radiation to the right shoulder. Examination now revealed a large, tender liver with a sharp, firm border. X-ray examination of the abdomen demonstrated diffuse calcification at the level of the second lumbar vertebra that was interpreted as being possibly in the right kidney. Barium-enema examination was negative. A Graham test showed poor visualization of the gall bladder. No calcified gallstones were seen. An adenomatous polyp was removed through the sigmoidoscope. Three months before admission the patient began to have more severe pain. The

pain started in the left upper quadrant, moving gradually to the right upper quadrant and thence to the right side over the lower ribs. It was constant and aching, was not associated with eating or bowel movements, was aggravated by standing, exertion and lying on the left side and was relieved by his lying on the right side. There was a 10-pound weight loss in the three months before admission. There was occasional vomiting shortly after overeating.

Physical examination was negative except for the presence of an enlarged liver, whose edge was palpable 10 cm. below the right costal margin, and which was firm and contained a questionable nodule.

The temperature was 99°F., the pulse 60, and the respirations 18. The blood pressure was 160 systolic, 100 diastolic.

Urinalysis was unremarkable. Examination of the blood revealed a white-cell count of 6100, with a normal differential. The hemoglobin was 13.0 gm. per 100 cc. The bilirubin was 0.5 mg., the alkaline phosphatase 7.0 units, the nonprotein nitrogen 34 mg., the albumin 4.6 gm., and the globulin 3.3 gm. per 100 cc. The prothrombin time was 60 per cent of normal. The cephalin flocculation was + in twenty-four and ++ in forty-eight hours. A bromsulfalein test showed 12 per cent retention of the dye in forty-five minutes. A blood Hinton test was negative. Two stool specimens gave negative guaiac tests. A tuberculin skin test with first-strength precipitated-protein derivative was positive. An echinococcus skin test and a complement-fixation test were negative. X-ray films and fluoroscopy of the upper gastrointestinal tract revealed thickened gastric folds and a duodenal deformity suggestive of a healed ulcer. A barium-enema examination was negative. Films of the chest showed advanced degenerative changes of the bones of the dorsal spine, calcified lymph nodes at the right hilus and linear streaking at both bases consistent with atelectasis. The oral Graham test showed poor visualization of the gall bladder. Intravenous and retrograde pyelograms revealed the upper abdomen to be filled and the transverse colon depressed by a large mass with a calcific rim (Fig. 1). The right kidney was displaced downward, with distortion of the calyceal system. The bladder showed good concentration of dye.

An aspiration biopsy of the liver was reported as negative. On the eighth day peritoneoscopy revealed a large, smooth, reddish-brown liver without visible metastases. On the undersurface of the right lobe there was a tongue of what appeared to be liver tissue extending in a circular manner for a distance of 8 to 10 cm. On the inferior surface of the left lobe there was also what appeared to be a projection of liver tissue extending 10 to 15 cm. in a semicircular manner. This tissue was a slightly lighter color than the remainder of the liver. A biopsy from this portion of the left lobe showed no diagnostic abnormality histologically. There was no evidence of cancer in the remainder of the peritoneal cavity. An exploratory laparotomy was performed on the twenty-seventh hospital day.

Differential Diagnosis

Dr. Gordon A. Donaldson*: This protocol presents a great many factual data, and it must be admitted that the case was well worked up before operation. As I went over it I thought there were two areas of disease present and that they were probably unrelated. The first, of course, was the carcinoma of the colon that had been removed six years previously. Dr. Fred Coller[1] has said that he has rarely seen carcinoma of the colon recur after a five-year interval had elapsed. I think that that has been our experience in this hospital. Of a small series of about 300 patients who have been carefully followed over the years, none have given evidence of recurrence of the carcinoma five years after operation. Four patients in the group died of recurrence after the five-year interval had elapsed, but in each case there was evidence of cancer before the five-year mark. There are exceptions, but I think our experience has got to influence my thinking about the patient under discussion. Of course, he could have had a new tumor of the colon, but I think this was ruled out by the repeated barium-enema studies. Polyps are frequently associated with carcinoma of the colon. Approximately 20 per cent of patients in this hospital undergoing resections of the colon have associated polyps in the large bowel. This patient had 3 in the original surgical specimen, and another was removed later. We do not know about the histology of that last one. It may have been fulgurated and could have been the focus of later metastasis to the liver.

The other area of disease was the liver. My problem is narrowed considerably by the fact that there was calcification in the tumefaction. I am going to rely heavily on Dr. Wang for help in the diagnosis of this lesion, which I think was a primary lesion unassociated with the previous carcinoma.

Dr. C. C. Wang: In the roentgenogram of the chest, the lungs are clear; no evidence of metastases is seen in the lung fields. There is some prominence of the left ventricle of the heart, and the aorta is somewhat tortuous. The right leaf of the diaphragm is unusually high. The films of the abdomen demonstrate multiple calcifications arranged in a ring measuring approximately 8 cm. in diameter over the right upper quadrant. On the oblique film the calcifications appear to lie within the liver. There is also an air-containing cavity in the liver, which was not recorded in the protocol. Intravenous and retrograde pyelograms show downward displacement of the right kidney but no definite abnormality of the calyceal system (Fig. 1). A barium-enema examina-

*Associate visiting surgeon, Massachusetts General Hospital.

tion gives no evidence of recurrent disease in the colon; the hepatic flexure is displaced inferiorly by what appears to be a mass in the liver. In the cholecystogram the gall bladder appears to function well; there is no evidence of stones. A gastrointestinal series shows only some prominent gastric folds and a deformed duodenal cap. The duodenal loop is not abnormal, and there is no evidence of a space-taking lesion in the pancreas.

DR. DONALDSON: This cavity within the mass bothers me; I am not sure that some of the conclusions I have made will be valid. For the intellectual exercise, I shall discuss the various causes of such calcifications in or near the liver. I have spoken of metastatic carcinoma of the colon with degeneration and subsequent calcification. These changes have been reported in metastatic carcinoma from the ovary, and the masses within the liver may become of considerable size. Most of the primary hepatic tumors or hepatomas that I have seen have been incidental and small, or have been large and very vascular. The large ones rupture either into the chest or into the abdominal cavity and give serious consequences. I believe hepatomas may calcify. Hemangioma occurs frequently in the liver and, as all hemangiomas do, may calcify in time. From the history we are led to believe that this tumor had been present for six years, although it is a little difficult to explain why symptoms had not been present consistently throughout the six years.

FIGURE 1. *Right Retrograde Pyelogram, Showing Downward Displacement of the Kidney, Presumably by an Extrinsic Renal Mass.*

DR. WANG: The calcification was not present in the first examination six years before the second admission.

DR. DONALDSON: It does not rule out the fact that a soft-tissue tumor might have been present, and from the history of pain in the right upper quadrant first noted six years before the second admission, I think we must conclude that disease had been present for some time.

A teratoma or a dermoid tumor is a possibility. Dermoids may calcify, but they are rare in the liver. Moreover, I believe the x-ray picture is likely to be that of miliary calcification. A gumma may present trabeculated calcium. Tuberculoma should be mentioned because there was evidence of tuberculosis elsewhere. The calcification at the level of the second lumbar vertebra may have represented tuberculous mesenteric lymph nodes, and we know that there were hilar lymph nodes that were calcified. The tuberculin test was positive. Tuberculomas, however, are usually small, as they are elsewhere, and do not resemble this enormous calcified mass in the liver. A pyogenic abscess or amebic abscess with calcification may be excluded by the past history and the appearance of the calcification.

An aneurysm, with bleeding and subsequent calcification, has been described in the hepatic artery and in the aorta, the latter displacing the liver forward. Aneurysm seems unlikely in view of the absence of any dramatic episodes in the past and the appearance of the present x-ray studies.

Echinococcus cyst was on the minds of the physicians who took care of this patient. Arce,[2] of Argentina, after over thirty years of experience with echinococcus cysts, concludes that the diagnosis of such a cyst in the liver is difficult to make and often is made only on the operating table. Our experience here is certainly limited. Bockus[3] reports that 95 per cent of the patients in this country with these cysts are foreign born. The patient under discussion fulfills this requirement. The right lobe of the liver is involved in 95 per cent of the cases. There was some question whether the left lobe of the liver in the patient under discussion was displaced on peritoneoscopy or whether both lobes were diseased. Eosinophilia is a frequent finding and the intensity of the eosinophilia depends on the activity of the parasite. In active cases an elevated eosinophil count is always found, and the level may range from 20 to 70 per cent. The white-cell count itself need not be elevated. The chemical tests of liver function are usually normal, and there is usually no anemia. The complement-fixation test and skin tests, however, are impressive evidence against an echinococcus cyst. Bockus notes positive complement-fixation tests in 80 per cent of his cases, and Arce positive tests in 60 per cent. The skin test is positive in 95 per cent of patients. So that although skin and complement-fixation tests do not eliminate the possibility of an echinococcus cyst, these results certainly make it unlikely. Are the x-ray findings consistent with an echinococcus cyst, Dr. Wang?

DR. WANG: The mass of calcifications does not look like a cystic structure.

DR. DONALDSON: The descriptions of echinococcus cyst call attention to a clear margin with a finer rim of calcium than is present in this case. One may, moreover, find calcified daughter cysts inside the main cyst. This area of decreased density does not look like that sort of thing.

Could this have been a simple, large, solitary cyst of the liver? Over 200 cases have been described in the literature up to 1950. These are nonparasitic and have an origin that is unknown. Some may be congenital; some may be retention cysts containing old blood, lymph or bile, and some may be the result of proliferating cystadenomas with degeneration and calcification. This seems to have been an extremely large cyst for such a process as a cystadenoma. Bockus states that solitary cysts are found in patients between the ages of forty and sixty and are more common in females, the ratio being 4:1. The lower inferior border of the right lobe is most often involved. Pain is present in 50 per cent of the patients only. Of course, a mass was palpable. The liver-function tests may be distorted, and I think the more-than-borderline levels in this patient were due to the space-occupying tumefaction and resulting compression of the liver substance. A certain number of these tumors produce actual jaundice. It is reported that these simple solitary cysts may calcify. They are often associated with cystic disease of other solid organs such as the spleen and kidneys. One of this patient's kidneys looked somewhat large in the x-ray film. It is said that 25 per cent of patients with polycystic kidneys have an associated cystic disease of the liver. In 1 patient whom we saw not too long ago most of the liver was replaced by a multitude of small, clear, fluid-filled cysts.

I think that this patient probably had a solitary cyst of the liver. The added information that Dr. Wang has given has confused me.

DR. THOMAS G. GABUZDA: I think that the mass within the liver that seemed like a shadow of air was caused by residual air left in the peritoneal cavity underneath the diaphragm after the peritoneoscopy, which preceded the x-ray films.

DR. WANG: I do not think that air is free in the peritoneal cavity; I think it is in the liver.

CLINICAL DIAGNOSIS

?Metastatic carcinoma of liver.

DR. GORDON A. DONALDSON'S DIAGNOSIS

Solitary calcified simple cyst of liver.

ANATOMICAL DIAGNOSIS

Adenocarcinoma, metastatic, of liver.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN A. BARNES: Preoperatively, on the Surgical Service, there was much speculation about the diagnosis. We thought that this mass in the liver probably represented a metastatic lesion that had taken a number of years to declare itself. A careful abdominal exploration revealed an entirely normal abdominal cavity except for the liver. The large bowel was entirely free of any lesion by palpation. The right lobe of the liver was replaced by a large spherical mass, which was covered by apparently normal liver tissue. Therefore, it was difficult to determine the exact nature of the tumor within the liver substance. An aspiration of the mass revealed cloudy material with much suspended particulate matter. Then a wider incision was made in the mass, and curettings were obtained. The curettings themselves were consistent with necrotic tumor that was lining a large cystic structure. No air was noted in the cavity at the time of operation.

DR. WINFIELD S. MORGAN: The rush frozen sections on the curettings were not very revealing, and the permanent sections on this material showed only necrotic material. However, sections of additional material taken at the time of operation showed adenocarcinoma typical of a primary tumor of the bowel. There were also masses of blue-staining calcification —the so-called dystrophic type of calcification. Similar calcification may be seen in caseous tuberculosis, atherosclerosis, fat necrosis and certain acute necrotic lesions such as pancreatitis, papillary tumors particularly and not rarely a variety of other tumors. Calcification of this degree, however, is certainly unusual. The deposition of calcium salts is not due to an increased blood calcium level but apparently is the result of a combination of certain local changes, especially of the pH. In a case such as this, we usually consider that the tumor does represent a metastasis from the original lesion that has perhaps been dormant for a while or is growing very slowly. I think it is fair to say that we are not quite so impressed with the idea that carcinoma of the bowel does not recur after five years. A patient seen recently in this hospital was found to have a single pulmonary metastasis eleven years after resection of a bowel carcinoma.

DR. DONALDSON: I think that the first signs of recurrence may appear after a lapse of five years but not often.

A PHYSICIAN: What is the present status of the patient?

DR. BARNES: The patient was discharged from the hospital and has been followed in the Out Patient Department. I have not seen him recently.

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GREATEST SHOW ON EARTH

THE American Medical Association, after more than three decades of wandering in strange lands and pitching its tents in distant places, will return to New England on November 29. Mechanics Building will be the Big Top; various hotels, hospitals and clinics will provide the side shows, and for the first time in history six states will jointly act as hosts. For New England, parched by its recent summer heat, inundated by floods, torn by tornadoes and rocked by hurricanes, liberally conservative in its philosophic acceptance of every type of visitation, throws open its historic confines to the fellows of the Association and their guests.

Although the members of only six state medical societies, acting through their hand-picked committees, have planned the scientific program, the speakers represent the cream of the country's crop. Among the guest artists will be interplanetary authorities on chemotherapy, cancer, seizures, anemia, the wide spectrum of diseases that can be erased at will by the adrenocorticotrophic hormones, and the problems of adolescence and those of industry, heart disease, poliomyelitis, surgical conditions and atoms for peace. From over 200 original papers submitted in nation-wide competition (more than the *Journal* receives in a month), 75 have been selected to be presented in twenty-minute periods followed by five minutes of eager and animated discussion.

Four clinicopathological conferences, each building up to its $64,000 question, will seek to stump the diagnostic experts; a television program emanating from the New England Deaconess Hospital, in which outstanding authorities in both medicine and surgery will expound the facts of life, will complement the major features of the program. A series of motion pictures has been selected to supplement in every possible way matters of greatest value to the physician. An extraordinarily special panel composed of unusually well qualified experts under the chairmanship of the president of the American Hospital Association will discuss modern medical training in a session so vibrant that the House of Delegates will be released from its legislative captivity in order to attend.

On the evening of Thursday, the kalends of December, the Boston Symphony Orchestra, under the direction of Dr. Charles Munch and through the courtesy of Winthrop-Stearns Company, will present a special program at Symphony Hall. A particularly important feature of the entire session will be an address to the House of Delegates by Mr. Robert Cutler, of Boston, recently assistant to President Eisenhower. Following a most meticulously selected motion-picture program Mr. Cutler's words will be piped like carbonated nectar to one of the city's larger auditoriums.

Consorts and marriageable daughters of the fellows will be provided for through the ample New England

hospitality of the Woman's Auxiliary of the Massachusetts Medical Society. A suite will be maintained for their entertainment at the Hotel Sheraton, where information, tea and coffee and powder rooms will be continuously available. A sherry party will be held for them at the headquarters of the Massachusetts Medical Society, the Museum of Fine Arts will hold specially conducted tours, and the town of Plymouth will re-enact the Landing of the Pilgrims, in costume, weather permitting.

GENES AND POLYPS

It is common knowledge that single polyps of the colon, apparently not of genetic origin, are noted in about 4 to 8 per cent of the general population and may at times predispose to cancer of this organ. This common type should not be confused with the rarer familial multiple polyposis of the colon, which is genetically controlled and has an extremely high propensity to malignant change at a much earlier age than cancer of the colon generally, nor with familial polyposis of the entire intestinal tract or small intestine.

In recent years some interesting forms of multiple polyposis apparently genetically associated with abnormalities elsewhere in the body have become established as distinct clinical entities.

In 1949, Jeghers, McKusick and Katz[1] delineated a syndrome in which distinctive melanin spots of the buccal mucosa and lips and occasionally of the face and digits were associated with polyposis limited to the small intestine or diffusely present throughout the entire gastrointestinal tract. This type of pigmentation does not occur with polyposis limited to the colon. Although sporadic cases have been noted the disorder is commonly familial, being inherited as a simple mendelian dominant that is not sex linked. There is evidence that the responsible genetic mechanism is a single pleiotropic gene, which is responsible for inheritance of both polyps and spots, rather than the association of two separate genes. The present status of this syndrome has been reviewed by Freeman and Ravdin.[2]

The fascinating concept of a genetic linkage of small-bowel intestinal polyps with a dermal lesion has been greatly broadened with the recent description of an entirely new syndrome linking multiple polyposis of the colon with osteomatosis and soft-tissue tumors. The paper by Weiner and Cooper in this issue of the *Journal* confirms the original presentation of this disorder by Gardner[3] in 1951, Gardner and Plenk[4] in 1952 and Gardner and Richards[5] in 1953, adding weight to the concept that it is a specific clinical entity.

This syndrome consists of multiple polyposis of the colon in association with "soft tumors" (epidermoid cysts, poorly defined connective-tissue masses or fibromas), located cutaneously or subcutaneously and usually detectable on physical examination, and "hard tumors" (multiple osteomas), detectable by x-ray study and often by physical examination. The soft-tissue tumors are occasionally absent or present in a latent form, becoming manifest in a traumatized area. There is evidence that these seemingly separate disorders are not fortuitously associated but in some mysterious manner linked genetically. As with the two features of the pigmentation-polyposis syndrome there appears to be a dominant mode of inheritance for all three manifestations of abnormal growth of this new syndrome. It occurs in either sex and may be due to a single pleiotropic gene, with the alternate possibility that it results from the association of two or three closely linked genes.

Pigmentation seems specifically linked with multiple polyposis of the small bowel or the entire intestinal tract whereas the "hard" and "soft" tumors have a suggestive genetic linkage with multiple polyposis of the colon, a point requiring observation of many more cases to be established with certainty.

Aside from the strong genetic implication these syndromes have an important clinical significance in the tendency of polyps in both disorders to undergo malignant changes. The pigment spots as well as the "hard" and "soft" tumors are present early in life, and their ready detection by clinical inspection or x-ray examination can serve as an indication for the presence of polyps, especially in other members of an involved family group. In a sense these external features may serve as an early warning of a possible future cancer of the intestinal tract in familial cases.

Once generally known to the medical profession, the new syndrome of "hard and soft" surface tumors associated with multiple polyposis of the colon may prove to be, as was true for the pigmentation-polyposis syndrome, more frequent than the few early reports suggest.

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ETIOLOGY OF GOITER

The paper by Bell and Eisenbeis published in this issue of the *Journal* presents a frequent enigma in medicine—the etiology of goiter in a nongoiter area. The case studies re-emphasize two practical points in the management of such patients: that a high uptake of radioactive iodide by the thyroid gland does not always mean hyperthyroidism; and that thyroid sur-

gery, short of total thyroidectomy, is not the answer to this problem. Reference is made to the complete disappearance of goiters by the administration of desiccated thyroid. However, some of these nontoxic nodular hyperplastic goiters are of long duration and from their pathology would not be expected to regress to any great degree with the administration of desiccated thyroid.

With the use of radioactive iodide, an entire spectrum of defects has been demonstrated in the metabolism of iodide by these goiters. Some are abnormally avid for iodide, some are unable to convert the concentrated iodide to the normal organic iodine moieties, some retain the concentrated iodide tenaciously, and others discharge it rapidly. Recently, it has been found that some goiters release into the circulation iodinated amino acids other than those that are assumed to be normal serum protein-bound moieties. The nature of these defects remains unknown.

The onset of this type of goiter at an early age suggests that the defect may be congenital. Hence, a careful inquiry into the patient's prenatal environment is warranted and may prove fruitful. The report of Stanbury and Hedge[1] demonstrates that intermarriage may be involved in the development of sporadic goiter. The familial occurrence of such goiters suggests that environmental factors may be important. However, it is doubtful if foodstuffs or various medications that are goitrogenic are primary factors in the goiter problem under discussion.

Since many of the functions of the thyroid gland are probably enzymatically controlled, the defects in some of these goiters may lie in the field of enzymology. Dennis, Wade and Trunnell[2] have made a histochemical study of embryonic, adult nodular and neoplastic thyroid tissue. The evidence suggests that there may be an alteration in enzyme systems in some of the nodular thyroid tissues containing only incompletely iodinated amino acids. This type of study should prove fruitful with the development of specific and refined methods of detecting the thyroid enzymes.

The thyroid gland is readily accessible and is frequently removed, and yet little progress has been made in defining this "goiter" since the initial studies by Hamilton et al.[3] in 1943. The solution might be hastened by an awareness of the problem by and a close co-operation between family physician, obstetrician, pediatrician, endocrinologist, surgeon, pathologist and biochemist.

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A ROSE BY ANY NAME

THE editor of the *Practitioner*, in a leading article published, appropriately, in the issue of July, 1955, devoted to diet and nutrition, discourses pleasantly on the character and definition of "sweetbread." The editor had apparently been taken gently to task — by a veterinary surgeon — for describing pancreas as sweetbread, a designation that the critic claimed applied only to thymus.

A minor amount of academic research revealed that according to medical standards and the *Shorter Oxford English Dictionary* as well, the term sweetbread is applied to both glands, the *Dictionary* further stipulating that it is "the pancreas or the thymus gland of an animal." The veterinarians, more rigid, stick to the thymic hypothesis, although the chief veterinary officer of Newcastle upon Tyne concedes that the pancreas is sometimes erroneously referred to by butchers as "gut sweetbread"; he even believes that "a local authority might be justified in taking action against a vendor who sold pancreas as 'sweetbread,' on the grounds that 'the food so described was not of the nature, quality, and substance demanded.' "

There is apparently in Scotland no legal definition of sweetbread; although thymus is implied by the term, the substitution of pancreas for thymus would not be actionable; a professor of the Royal Veterinary College handed down the opinion that although sweetbread is traditionally thymus, common usage has included pancreas in the general term. Apparently, some legal clarification is called for when the British Food and Drugs Act next comes up for revision.

In the United States sweetbread is more specifically defined by Webster as "the thymus or pancreas of any animal (esp. a calf) used for food, the former being the *throat sweetbread* or *neck sweetbread*, the latter the *stomach sweetbread*." Dorland agrees, adding to the category the testes of animals when used as food. Stedman agrees with Dorland in including the thymus and the pancreas, but delicately omits the testes; the *New Gould Dictionary* ignores the entire subject, passing from "sweeny — A wasting or atrophy of the scapular muscles of the horse" to "swelling — Any morbid enlargement, inflation or abnormal protuberance."

We have received a specimen of a plan for the "easy record and preservation of certain important particulars in the cases that occur to every physician in his private practice," arranged by Dr. Wm. Henry Thayer, of Woodstock, Vt., Secretary to the Vermont Medical Society and which is about to be issued under the authority of that Society.

Boston M. & S. J., *Nov. 15, 1855*

BOSTON MEDICAL LIBRARY

FREE MAILING SERVICE FOR MEMBERS

Effective November 1, 1955, all postage and insurance charges for books ordered by members of the Boston Medical Library and sent through the mail are being defrayed by the Library.

When books are mailed to a member, he will receive under separate cover an explanatory letter, a self-addressed label for sticking on the return package, adequate postage and a self-addressed return postal card, which he will fill out and drop in the mail when he mails the books back to the Library. The return postal card is required by the insurance company that is insuring the books on their return trip.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

BACTERIOLOGIC DIAGNOSIS OF TUBERCULOSIS

To promote better utilization of the existing facilities in the Commonwealth for the laboratory diagnosis of tuberculosis, a special *ad hoc* committee consisting of clinicians and members of the Massachusetts Department of Mental Health, Massachusetts Department of Public Health, Massachusetts Medical Society and Massachusetts Tuberculosis and Health League, after a series of deliberations, has prepared the recommendations given below as a guide to physicians in the diagnosis and treatment of cases or suspected cases of tuberculosis.

Services at Diagnostic Laboratory

The Diagnostic Laboratory of the Massachusetts Department of Public Health, which co-operated in the preparation of these recommendations, is encouraging adherence by distributing for a time copies of the report with its packages of outfits, and by modifying its outfits so that the new recommendations can be easily followed by both the physician and the Diagnostic Laboratory. For instance, outfits containing carbolic acid for the direct microscopical examination of smears for tuberculosis are no longer distributed, and only outfits containing no carbolic acid are given out. In this way, either direct smear or culture examination may be performed on the specimen, and will be done in accordance with the second paragraph under section 2 below entitled, "Routine Laboratory Examination of Sputum." As indicated, if the three separate sputum specimens on three successive days are submitted as advised, all three specimens will be examined by direct smear. The first specimen will be cultured whether it is positive, doubtful or negative on microscopical examination. In addition, the second specimen will be cultured if the first smear is negative or doubtful on microscopical examination. The third specimen will be cultured if the first two smears are negative or doubtful on microscopical examination.

Recommendations

1. Outfits and Instructions:

Sputum outfits should contain no bactericidal agents, since a specimen sent in for a direct examination may still need to be cultured.

In order to facilitate use, the mouth of a sputum specimen bottle should be at least one inch in diameter.

Doctors and Nurses should give careful directions to patients to collect only sputum COUGHED UP FROM THE LUNGS. Saliva or post-nasal discharge is unsatisfactory for examination.

Outfits for gastric specimens should contain a buffer for purposes of neutralization.

Plans should be made so that specimens will not arrive at the laboratory on Saturdays, Sundays, or holidays.

2. Specimens Submitted for *Diagnosis of Tuberculosis:*

Collection of Sputum. It is recommended that physicians submit to the laboratory three separate sputum specimens collected on three successive mornings. All sputum specimens should be coughed up from the lungs from the time of waking until after breakfast unless the only sputum raised is later in the day. Each specimen should be sent to the laboratory immediately.

The value of obtaining specimens by bronchoscopy in certain cases should not be overlooked.

Routine Laboratory Examination of Sputum. All three specimens should be examined by direct smear. The first specimen should be cultured whether it is positive, doubtful, or negative by microscopic examination. In addition, the second specimen should be cultured if the first smear is negative or doubtful by microscopic examination. The third specimen should be cultured if the first two smears are negative or doubtful by microscopic examination.

Fasting Gastric Contents. Fasting gastric contents should be collected on three successive days if no sputum is obtained, if the specimen is insufficient in quantity, or if the sputum is repeatedly negative. The undiluted gastric contents should be obtained first. The best results appear to be obtained when, in addition to the fasting contents, the stomach is lavaged afterward with sufficient tap water to bring the total aspirated fluid up to approximately 100 cc. The gastric specimen should be collected in the morning before the patient rises. The patient should not brush his teeth with a dentifrice, nor should the gastric secretions be stimulated by smoking or the smell of foods. Because prolonged standing may make the recovery of tubercle bacilli by culture impossible, each specimen should be sent to the laboratory immediately in a container having the proper buffered solution supplied by the laboratory. Direct microscopic examination of gastric specimens is not recommended, because acid-fast organisms that are not tubercle bacilli may be found.

Spinal Fluid Examination. 5 to 10 cc. of spinal fluid should be collected under sterile precautions.

a. The fresh spinal fluid should be examined for total and differential cell count, for total protein and sugar. Do locally; do not send to State Laboratory. Routine culture for non-tuberculous organisms should be done on centrifuged specimen.

b. If possible, at least 5 cc. of spinal fluid should be sent without delay to the laboratory for smear and culture for tubercle bacilli.

c. In doubtful cases a second spinal fluid for culture should be submitted.

d. Subsequent spinal fluid specimens during treatment should be submitted at the discretion of the physician.

e. It should be stressed that whenever the clinical picture is consistent with that of tuberculous meningitis, appropriate treatment should be started immediately without awaiting results of culture.

Urine Specimens. Urine specimens for examination for tubercle bacilli should be collected as follows:

a. No fluids should be taken by mouth after 6 p.m. until the completion of the test.

b. Discard specimen voided just before retiring.

c. Save and keep as cold as possible all urine passed after midnight, as well as the first morning specimen, for laboratory examination.

d. Specimens should be sent to the laboratory at once, as the urine is toxic to tubercule bacilli and overgrowth by contaminants may occur.

e. The specimen should be a "clean" voided specimen or one collected by catheterization.

f. Catheter or cystoscopic specimens should be clearly identified as such. Right or left ureteral specimens should be carefully labeled in separate sterile tubes. Because mix-ups have occurred in the past, the Diagnostic Laboratory recommends that the cystoscopist should personally check that the specimen from the right ureter actually goes into the tube so labeled, and so forth.

Other Body Fluids. All types of body fluids should be carefully identified. Pleural, peritoneal, and synovial fluids should be sent to the laboratory in as large amounts as possible that can be contained in the appropriate outfits obtainable from the laboratory.

3. Routine Recommended for Examination of Specimens *During the Treatment of Tuberculosis*:

In the absence of sputum, a gastric specimen should be collected as instructed above every six to eight weeks during treatment. If sputum is positive by direct smear, repeated cultures are not necessary.

Drug sensitivity tests should be done if laboratory facilities are available.

After termination of chemotherapy, specimens should be collected every three months as long as any question of activity remains.

Culture of specimens should constitute the routine bacteriological technic. Guinea pig inoculation should be done as the laboratory finds it necessary and in especially important diagnostic problems.

Both clinicians and the laboratory should be alert for possible mycotic infections, including Nocardia asteroides, which may simulate tuberculosis but require different handling in the laboratory.

It is hoped that physicians caring for tuberculous patients and patients suspected of having tuberculosis will follow these recommendations as fully as circumstances permit.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1955

RÉSUMÉ

Disease	Sept. 1955	Sept. 1954	Seven-Year Median
Chancroid	1	0	2
Chicken pox	39	56	87
Diphtheria	0	1	2
Dog bite	1229	1236	1050
Dysentery, bacillary	24	11	11
Encephalitis, infectious	2	1	1
German measles	35	39	58
Gonorrhea	154	198	199
Granuloma, inguinale	0	0	0
Hepatitis, infectious	65	95	29*
Lymphogranuloma venereum	0	0	1
Malaria	1	2	2
Measles	48	275	97
Meningitis, meningococcal	3	10	4
Meningitis, Pfeiffer bacillus	1	1	2
Meningitis, pneumococcal	1	0	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	5	7	3
Mumps	90	274	274
Poliomyelitis	1008	350	177
Salmonellosis	20	20	11
Scarlet fever	46	59	59
Syphilis	161	131	140
Trichinosis	1	0	3
Tuberculosis, pulmonary	154	200	189
Tuberculosis, other forms	8	16	9
Typhoid fever	0	3	2
Undulant fever	3	1	1
Whooping cough	55	184	191

*Six-year median.

COMMENT

Diseases below the seven-year median were chicken pox, diphtheria, German measles, measles, mumps, scarlet fever and whooping cough.

With but one exception (1954) chicken pox was at the lowest level during September than for the corresponding month of any year since 1922.

The figures listed for German measles and mumps make these the lowest for these diseases for the month of September since 1944 and 1939 respectively.

During September scarlet fever and whooping cough were at their lowest levels for this month in the history of the State.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis, poliomyelitis and salmonellosis.

During September poliomyelitis was at the highest level for this month in the State's history.

Though above the median, infectious hepatitis during September was at the lowest level in three years.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Dysentery, bacillary: Belmont, 1; Boston, 11; Fitchburg, 2; Lowell, 1; Waltham, 9; total, 24.

Encephalitis, infectious: Boston, 1; New Bedford, 1; total, 2.

Hepatitis, infectious: Andover, 3; Boston, 6; Cambridge, 3; Chelmsford, 1; Chelsea Naval Hospital, 3; Chicopee, 2; Fall River, 2; Lowell, 2; Ludlow, 1; Medford, 1; Methuen, 1; Millbury, 1; Natick, 1; Needham, 1; New Bedford, 1; Springfield, 6; Tewksbury, 2; Tewksbury State Infirmary, 27; West Springfield, 1; total, 65.

Malaria: Amherst, 1.

Meningitis, meningococcal: Northampton, 1; Salem, 1; Springfield, 1; total, 3.

Meningitis, Pfeiffer bacillus: Woburn, 1.

Meningitis, pneumococcal: Gloucester, 1.

Meningitis, undetermined: Cambridge, 1; North Andover, 1; Pittsfield, 1; Springfield, 2; total, 5.

Poliomyelitis: Abington, 4; Acton, 3; Amherst, 9; Andover, 2; Arlington, 13; Athol, 1; Attleboro, 11; Auburn, 1; Barnstable, 9; Barre, 3; Bedford, 6; Bellingham, 4; Belmont, 2; Berlin, 1; Beverly, 10; Billerica, 2; Boston, 163; Bourne, 3; Braintree, 10; Brewster, 1; Brockton, 15; Brookline, 11; Burlington, 1; Cambridge, 20; Canton, 5; Charlemont, 1; Chatham, 1; Chelsea, 4; Chicopee, 8; Clarksburg, 1; Clinton, 1; Cohasset, 3; Colrain, 4; Concord, 4; Danvers, 8; Dartmouth, 3; Dedham, 5; Dennis, 1; Dighton, 3; Douglas, 1; Dracut, 1; Duxbury, 2; East Bridgewater, 1; East Longmeadow, 2; Eastham, 2; Easton, 3; Edgartown, 2; Essex, 1; Everett, 3; Fairhaven, 1; Fall River, 15; Falmouth, 3; Fitchburg, 7; Foxboro, 1; Framingham, 12; Franklin, 3; Gardner, 1; Georgetown, 2; Gloucester, 4; Grafton, 1; Greenfield, 2; Groveland, 2; Halifax, 1; Hamilton, 3; Hanover, 1; Hanson, 1; Haverhill, 8; Hingham, 8; Holbrook, 2; Holden, 3; Holliston, 4; Holyoke, 1; Hopedale, 2; Hopkinton, 1; Hull, 8; Ipswich, 1; Kingston, 8; Lawrence, 4; Leominster, 2; Lexington, 3; Lincoln, 1; Lowell, 5; Ludlow, 1; Lynn, 18; Lynnfield, 3; Malden, 10; Mansfield, 3; Marblehead, 1; Marion, 3; Marshfield, 4; Maynard, 2; Medfield, 2; Medford, 14; Medway, 3; Melrose, 12; Mendon, 4; Merrimack, 1; Middleboro, 2; Milford, 24; Millbury, 1; Millis, 1; Millville, 1; Milton, 1; Nahant, 1; Nantucket, 1; Natick, 9; Needham, 9; New Bedford, 20; Newburyport, 1; Newton, 25; North Adams, 2; North Andover, 1; North Attleboro, 2; North Brookfield, 1; North Reading, 1; Northampton, 9; Northbridge, 3; Norton, 4; Norwell, 1; Norwood, 5; Orleans, 1; Oxford, 1; Peabody, 15; Pelham, 1;

Pembroke, 3; Pepperell, 1; Pittsfield, 6; Plainville, 2; Plymouth, 15; Princeton, 1; Quincy, 25; Randolph, 7; Reading, 6; Rehoboth, 1; Revere, 2; Rockport, 1; Salem, 14; Saugus, 2; Scituate, 8; Seekonk, 1; Sharon, 1; Shelburne, 1; Shrewsbury, 2; Somerset, 1; Somerville, 17; South Hadley, 3; Southboro, 1; Southbridge, 5; Spencer, 2; Springfield, 8; Sterling, 2; Stoneham, 5; Stoughton, 1; Sudbury, 1; Swampscott, 7; Swansea, 1; Taunton, 5; Tewksbury, 4; Topsfield, 2; Truro, 1; Upton, 6; Wakefield, 5; Waltham, 15; Wareham, 6; Watertown, 11; Webster, 1; Wellesley, 6; Wenham, 2; West Springfield, 2; West Stockbridge, 3; Westborough, 3; Westfield, 1; Westport, 1; Westwood, 5; Weymouth, 16; Williamstown, 6; Wilmington, 3; Winchendon, 2; Winchester, 1; Winthrop, 10; Woburn, 6; Worcester, 11; Yarmouth, 1; total, 1008.

Psittacosis: Northampton, 1.

Salmonellosis: Boston, 7; Cambridge, 1; Fitchburg, 1; Lexington, 1; Marshfield, 1; Medford, 1; Quincy, 1; Springfield, 1; Stoneham, 1; Watertown, 1; Weston, 1; Woburn, 1; Worcester, 2; total, 20.

Trichinosis: Boston, 1.

Undulant fever: Cambridge, 1; Oxford, 1; Shutesbury, 1; total, 3.

CORRESPONDENCE

TREATMENT OF PITUITARY ADENOMAS

To the Editor: I am writing to you concerning the article, "Present-Day Treatment of Pituitary Adenomas: Surgery versus x-ray therapy," by Horrax, Smedal, Trump, Granke and Wright, which appeared in the March 31 issue of the *Journal*, and was abstracted in the *Journal of the American Medical Association* in June. The authors conclude that the necessity of surgical interference in the treatment of pituitary tumors was lessened by the use of rotational therapy with the 2,000,000-volt apparatus. The abstract that appeared in the *Journal of the American Medical Association* says that these results "show the tremendous gain effected by the new method of irradiation treatment."

To the casual reader unacquainted with the principles of radiation physics, these results may appear striking. However, another interpretation may be possible. I should like to point out the following three factors, which I think somewhat vitiate the exceptional results claimed in the article.

It is stated that from November 1, 1932, through December 31, 1953, 303 patients were admitted to the Lahey Clinic with the diagnosis of either a chromophobe or a chromophil pituitary adenoma. Furthermore, in the period 1932 to 1949 inclusive, a total of 125 patients were treated by surgery only, or surgery combined with radiation. In the same period, 173 patients were treated by radiation only, or were operated on because they had received no benefit from radiation. Then, in the recent four-year period, 1950 to 1953 inclusive, a total of 63 patients of both types were seen and treated. This gives a total of 361 patients. It is logical to ask whence the additional 58 patients appeared. This number is identical with the number given in the first series who were said to have required operation because x-ray treatment was not effective.

It was the policy in many hospitals in the period during which investigation was carried out to combine radiation and surgery in the treatment of these tumors. Dr. L. M. Hurxthal, of the Lahey Clinic, writing in the *Surgical Clinics of North America* (**27**:530-534, 1947), states, "Immediate post-operative radiation is customary in chromophobe and chromophil tumors, or in other tumors which are considered malignant or radiosensitive."

Also in the *Surgical Clinics of North America* (**31**:877-881, 1951) Horrax has given a report on the "Chromophobe Pituitary Adenomas: Surgical and radiation treatment." In this article he reports on a series of 105 verified chromophobe adenomas from 1932 through 1949. It is evident that the smaller series appearing in the *Surgical Clinics of North America* is a component part of the first group (chromophobe plus chromophil adenomas) reported in the *New England Journal of Medicine*. Regarding the verified chromophobe adenomas it is stated that in only 36 of the 60 patients who had combined surgery and radiation, operation became necessary because of the failure of x-ray treatment to hold vision to a useful level. Therefore, at least 24 of these patients received radiation and surgery as part of a combined plan rather than surgery because of a failure of radiation. Since this refers only to the chromophobe adenomas, would not a similar number be present in the chromophil series? If these 24 cases are subtracted from the 58 cases, the need for postirradiation surgery is less striking in the first series (approximately 34 per cent according to the authors' methods of calculation).

The second item I question in this study concerns the relative frequency of visual disturbance found in the two series. In the period from 1932 to 1949 there were 173 patients (not operated on primarily) who had chromophobe or chromophil adenomas. Of these, 74 had no visual loss, and 99 were said to have had visual loss — thus, 42.6 per cent of the 173 patients had no visual loss. In the second series given x-ray treatment from 1950 to 1953 inclusive, the total number of patients was 53, of whom 15, or 28.4 per cent had no visual loss, and 38 had evidence of visual loss. Do these two groups of patients represent samples from the same population? If the samples are not homogeneous, one may question whether they are random samples. If the samples are not random and comparable, a serious error is introduced.

In the first group of 173 patients, of whom 42.6 per cent had no visual loss, the confidence limits were the 99 per cent band on the basis of a binomial expansion, as follows: the lower limit of the parent population is 33 per cent, and the upper limit is 50 per cent. The presence of 28.4 per cent with no visual loss in the second group is therefore below the lower limit. These figures were obtained from the tables given by Mainland in *Elementary Medical Statistics: The principles of quantitative medicine* (Philadelphia: Saunders, 1952), showing the binomial confidence limits.

The standard error for the difference between two proportions can be calculated by means of the following formula, taken from A. Bradford Hill's work, *Principles of Medical Statistics* (London: Lancet, 1948):

$$\sqrt{\frac{p \times q}{N_1} + \frac{p \times q}{N_2}}$$

This calculated standard error of the difference is 7.25. The difference in percentage of the two samples is 42.6 minus 28.4, or 14.2. This figure is almost twice the standard error of the difference so that the probability that these samples were taken from the same population is close to 0.05.

These mathematical tests indicate that the samples may have been taken from two different populations, but this is not reasonable since there has been no change in the biologic behavior of pituitary tumors. A more likely explanation is that the criteria for the division of patients into two groups — with visual loss and without visual loss — has varied over the period of observation. It may be that ophthalmologic investigation in recent years has been more precise. In any event, there are more patients with visual loss in the second group, and this group may include patients with very minor changes. If this assumption is correct the second group includes the earlier and smaller lesions that would be expected to respond to the cytolytic effects of x-rays much more readily, particularly since this effect is measured by the absence of further impairment of vision.

A third objection that might be raised to the figures is the method by which the percentage of results is calculated and presented. In the paper the authors state that 58 per cent of the first group of 99 patients with visual loss required operation whereas only 7 patients, or 18.4 per cent, of the 38 patients in the second group required operation. When calculated in this manner the difference is indeed striking. A sounder method would have been to have based the percentage on the total number of patients with pituitary adenoma seen during each period. The percentage should be based on population at risk, and any patient with a

pituitary adenoma is subject to possible optic-nerve pressure. If the total number of patients were made the denominator of this fraction, the difference in percentages would be reduced by almost half.

Two further but minor criticisms may well be raised. In less than half the patients in the entire series was the diagnosis established by histologic means. If this frequency is distributed equally in both groups possible errors in diagnosis would be represented equally in both samples. However, it is not clear from the paper whether this is so. Furthermore, the second group was followed only for a period of eight months to four years, and this is too short a time for one to evaluate the efficiency of any therapy in pituitary tumors.

For the reasons given above, I believe the reader may reasonably question the validity of the assumption that this study indicates the superiority of rotation of the patient, of a 2,000,000-volt apparatus at the Massachusetts Institute of Technology and of a tumor dose of 4000 r.

Until further and more convincing evidence is presented, the results with properly given orthovoltage radiation therapy must be considered equally satisfactory.

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Dr. McCort's letter was submitted to the authors of the paper in question, one of whom offers the following reply:

To the Editor: I have been asked to express the reactions of the authors to Dr. McCort's criticisms, which I have read over very carefully.

The first point he brings up concerns the total number of patients treated, referring to the 125 patients who were treated by surgery only or surgery combined with radiation and the 173 patients who were treated by radiation only or were operated on because they had received no benefit from radiation. He has added these two figures, which refer to the patients treated before 1950, to the 63 patients who were seen and treated from 1950 to 1953 inclusive, which makes, as he says, a total of 361 patients, rather than the 303 total that we indicated. What Dr. McCort did not realize and perhaps what we did not make clear in our statement in the article was the fact that among the 173 patients who were treated by radiation only or were operated on because they received no benefit from radiation were the 58 patients who had received no benefit from the radiation and therefore had to be operated upon, and these, of course, were included in the 125 total of patients who were treated by surgery only or surgery combined with radiation. Subtracting this number (58) from the total of 361 obviously makes the 303 patients on whom our paper is based. It is possible that we should have put in another table to make this clearer, but in any case, that is why the discrepancy occurred.

Dr. McCort goes on to say that Dr. Hurxthal mentioned in some article that immediate postoperative radiation is customary in chromophobe and chromophil tumors. This, of course, is perfectly true and it is well known to be customary, but I do not quite see the point of this remark.

He then refers to an article that I wrote in the *Surgical Clinics of North America,* referring to 105 verified chromophobe adenomas, from 1932 through 1949, in which it is stated that in 36 of the 60 patients who had combined surgery and radiation operation became necessary because of the failure of x-ray treatment to hold vision at a useful level. This represents exactly 60 per cent of the patients who had to be operated on because of the failure of radiation in that period, which is a figure very close to the final one in our whole series of pituitary adenomas — namely, 58.5 per cent. Therefore, I see no particular discrepancy there.

His next comment is regarding the percentage of visual disturbances found in two series to which we have referred; he has noted a discrepancy in the figures in the two groups — namely, 42.6 per cent of the patients in the first group who had no visual loss and 28.4 per cent of those in the second group who had no visual loss — and asks whether these two groups of patients represent samples from the same population. All I can say to this is that these are the figures taken from our total series of 303 pituitary adenomas, and, for what they are worth, they simply mean to me that, in the earlier period, more patients came for treatment to us with no visual loss in that period, whereas in the second period the percentage was considerably lower.

Regarding his comment concerning certain mathematical principles involved in the computation, I can only say that I do not feel competent to deal with these in any way, and he refers to what he calls samples that may have been taken from two different populations or other variants that he mentions. There were, of course, no differences in the population under discussion. All the patients were those who came here for the relief of their pituitary or visual deficiencies.

His comment about the method by which our percentage results were calculated does not seem logical to me for the following reasons: what we were trying to do in this paper was to see what percentage of patients who actually needed operation, or were at least thought to need operation, were benefited by x-ray treatment or if not benefited had to be operated on because of the failure of x-ray treatment. The basis for the operative treatment of pituitary adenomas in the vast majority of cases has always been the question of failing vision, and it was for this reason that we subtracted the number without visual loss who were given x-ray treatment only for other purposes.

I am sure that all those who have dealt with pituitary tumors on a large scale would consider this the correct way of presenting figures for this purpose. The ones with visual loss were the only patients who would perhaps need to be operated on.

Regarding the question of verified and unverified tumors in the entire series, no specific figures were given for that for each group of cases presented, but we have the figures for these and they are as follows: in the period 1932 to 1949 inclusive, there were 125 verified tumors and 115 unverified — that is, those having a large sella turcica and other stigmas of pituitary adenoma. In the group from 1950 to 1953 inclusive, there were 18 verified tumors and 45 unverified except by the criteria mentioned. This discrepancy appears to be due almost entirely to the fact that in the second period no chromophil tumors were operated on, either because this was not necessary or because we did not happen to have as many in that period proportionately as we had in the first period.

As for Dr. McCort's final criticism, which concerns the fact that the second group of cases were only followed for a period of eight months to four years, I may say that, of course, we were perfectly aware of this fact and that is why we made the statement in the paragraph in our article just before the discussion: "Although the length of time since the treatment only runs up to four years . . . ."

Dr. Smedal has made the comment that, although Dr. McCort says, "To the casual reader unacquainted with the principles of radiation physics, these results may seem striking," there appears to be no inkling of what the principles of radiation physics have to do with his argument. Dr. Smedal says further that, since Dr. McCort questions the validity of the assumption that this study indicates the superiority of rotation of the patient, of a 2,000,000-volt apparatus at the Massachusetts Institute of Technology and of a tumor dose of 4000 r, it would have been logical for him to have specified his technic of treatment and also the results in his personal series of cases, subject to the same probability analysis, of course.

In conclusion, I can only say that we have tried to make a careful evaluation of the various kinds of treatment that we have employed during the past twenty years — both of operative therapy and of the types of x-ray therapy that have differed during the two periods indicated. Certainly, we, at least, are convinced that rotational therapy with a 2,000,000-volt apparatus delivering a 4000-r tumor dose has so far given us results considerably superior to those obtained in the period before 1950.

GILBERT HORRAX, M.D.
Boston

REGARDING PHENYLBUTAZONE

To the Editor: There appears to be an inconsistency between the excellent article on the toxic effects of phenylbutazone (Butazolidin) by Mauer in the September 8 issue of the *Journal*, the fine editorial, "Not to Harm," and the full-page advertisement (in two colors) of Butazolidin. For consistency's sake at least, would it not be best to withdraw further advertising of this product from our esteemed *Journal*?

WILLIAM DAMESHEK, M.D.

Boston

Note: The *Journal's* committee on advertising withheld approval of phenylbutazone until some time after it had been accepted by the Council on Pharmacy and Chemistry of the American Medical Association. It was then approved because of its recognized clinical value and the willingness of the manufacturers of Butazolidin to insert in their advertising text a warning to physicians to familiarize themselves with the use of the drug before instituting therapy.
ED.

SOCIAL SECURITY FOR PHYSICIANS

To The Editor: Regarding the editorial, "Hell-Bent for Election," in the September 8 issue of the *Journal*, I think that there should be a national poll of physicians by the A.M.A. on the controversial issue of social-security coverage for doctors.

If the A.M.A. fears the result of such a poll it should be conducted on a state-society level to find the actual views of the physicians themselves.

MILTON PEASE, M.D.

Brookfield, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Method of Balanced Anesthesia in General Surgery, Obstetrics and Dentistry. By Sylvan M. Shane, D.D.S., attending anesthesiologist, Lutheran Hospital of Maryland, chief of anesthesiology, Doctors Hospital of Baltimore, and consultant in anesthesiology, Spring Grove Hospital of Maryland; and Harry Ashman, M.D., chief of anesthesiology, Lutheran Hospital of Maryland. 8°, cloth, 53 pp., with 2 illustrations. Baltimore: Lowry and Volz, 1955. $2.25.

This monograph describes the method of anesthesia used by the authors in over 20,000 patients during six years. A list of references is appended to the text.

Neuro-Ophthalmology. By Donald J. Lyle, M.D., professor of ophthalmology and director, Department of Ophthalmology, University of Cincinnati College of Medicine, director, Ophthalmologic Service, Cincinnati, Dunham, Drake and Children's hospitals, attending ophthalmologist to Good Samaritan and Christ hospitals, chief clinician, Ophthalmologic Service Outpatient Department, Cincinnati General Hospital, consulting ophthalmologist to the Children's Convalescent Home, Cincinnati, and senior consultant to Veterans Administration Hospital, Dayton, Ohio. Second edition. 4°. cloth, 591 pp., with 335 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $17.50.

This new edition of a book first published in 1954 and twice reprinted has been revised. Lists of references are appended to the chapters, and there is a good index. The publishing, especially the illustrative work, is excellent. The book should be in all collections on neurologic ophthalmology.

Treatment of Acute Poliomyelitis. Edited by William A. Spencer, M.D., from the departments of Pediatrics, Physiology and Physical Medicine, Baylor University College of Medicine, Southwestern Poliomyelitis Respiratory Center, Jefferson Davis Hospital, in co-operation with the National Foundation for Infantile Paralysis, Incorporated. Second edition. 4°, paper, 134 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.75.

This is a loose-leaf manual on the various aspects of the treatment of poliomyelitis. The material was prepared as a teaching aid and is the joint work of 22 persons.

Surgery for Dental Students. By Michael F. A. Woodruff, M.D., M.S. (Melb.), F.R.C.S. (Eng.), professor of surgery in the University of Otago, New Zealand. With a foreword by S. H. Wass, M.S. (Lond.), F.R.C.S. (Eng.), surgeon, Guy's Hospital, lecturer in surgery, Guy's Hospital Medical and Dental Schools, and staff examiner in surgery in the University of London. 8°, cloth, 326 pp., with 108 illustrations. Oxford: Blackwell Scientific Publications, 1954. 30s.

This book is based on a course of lectures delivered to dental students in the University of Sheffield. The text, which first considers the general subjects of a pathological character, concludes with a discussion of definite surgical conditions. The publishing is excellent, and the book should well serve its intended purpose.

Psychosurgery and the Self. By Mary Frances Robinson, Ph.D.; and Walter Freeman, M.D., Ph.D. 8°, cloth, 118 pp., with 11 tables. New York: Grune and Stratton, 1954. $3.00.

The authors discuss prefrontal lobotomy and its after-effects on the basis of a series of 51 cases compared with 17 control patients. The literature is surveyed, and there is a bibliography of 179 references.

Emotional Problems and What You Can Do about Them: First aid to wiser living. By William B. Terhune, M.D., medical director, Silver Hill Foundation, New Canaan, Connecticut, and associate clinical professor of psychiatry, Yale University School of Medicine. 12°, cloth, 190 pp. New York: William Morrow and Company, Incorporated, 1955. $3.00.

Dr. Terhune has based his book on an address that he gave during World War II. The text is divided into two parts. The first discusses the fundamentals of personal mental hygiene under the headings of psychologic preparedness and equipment, self-education, first aid for the adult, older people, children and the adolescent. The second describes the technics for meeting specific psychologic emergencies, such as how to break bad news gently and sympathetically.

The Spino-Cerebellar Degenerations. By J. G. Greenfield, M.D., F.R.C.P. 8°, cloth, 112 pp., with 2 figures, 3 charts and 3 tables. Springfield, Illinois: Charles C Thomas, 1954. $4.00. (Publication No. 244, *American Lecture Series.*)

Dr. Greenfield surveys and evaluates the pertinent literature on the various spinocerebellar degenerations. There is a bibliography of 24 pages arranged alphabetically by authors. The small book is recommended for all collections on neurology.

From Classical to Modern Chemistry: Some historical sketches. By A. J. Berry, M.A., 8°, cloth, 250 pp. Cambridge, Massachusetts: University Press, 1954. $4.75.

Mr. Berry furnishes a history of chemistry from ancient to modern times. There are indexes of names and subjects. The book should be in all history collections.

Zur Pathogenese des endogenen Ekzems. By Doz. Dr. Med. Günter Korting, Tübingen. With a foreword by Prof. Dr. H. A. Gottron, director, Univ.-Hautklinik, Tübingen. 8°, paper, 107 pp., with 23 illustrations and 18 tables. Stuttgart: Georg Thieme, 1954. DM 13.80.

The author surveys the literature of the pathogenesis of endogenous eczema. There is a solid bibliography of almost 9 pages. The monograph should be in all collections on dermatology.

Reactions with Drug Therapy. By Harry L. Alexander, M.D. 8°, cloth, 301 pp., with 33 illustrations and 23 tables. Philadelphia: W. B. Saunders Company, 1955. $7.50.

The author, in this monograph, discusses the various aspects of drug hypersensitivity. The literature is surveyed, and extensive bibliographies are appended to the chapters. There is a good index; the publishing is excellent. This is a valuable publication and is recommended to all medical libraries and to all interested persons.

The City of Hope. By Samuel H. Golter. 8°, cloth, 177 pp., with illustrations. New York: G. P. Putnam's Sons, 1954. $3.50.

This is the story of the unique nonprofit medical center developed at Duarte, California. Beginning in 1913 in the desert near Los Angeles, it has now developed into a multimillion-dollar group of clinics, hospitals and research laboratories. No patient is ever asked to pay a fee. It is a nonsectarian medical center, operated under Jewish auspices and supported by chartered auxiliaries and voluntary contributors.

Krankengymnastik in der Chirurgie. By Pro. Dr. med. Wolfgang Kohlrausch, Marburg and Freudenstadt, medical director, Sanatorium Hohenfreudenstadt. 8°, cloth, 101 pp., with 36 illustrations and 1 table. Berlin: Walter de Gruyter and Company, 1954. DM 16.-.

The author considers the use of medical gymnastics in various surgical conditions. The coverage is extensive, and there is a section on technic in which methods are illustrated. The publishing is excellent.

Psychoanalytic Interpretation in Rorschach Testing: Theory and application. By Roy Schafer, Ph.D., chief clinical psychologist, Department of Psychiatry, Yale University School of Medicine. 8°, cloth, 446 pp. New York: Grune and Stratton, 1954. $8.75. *(Austen Riggs Foundation Monograph Series* No. 3.)

This new book on the Rorschach test discusses the present status of the test. A large number of case histories are distributed throughout the text. The literature has been surveyed, and there is a bibliography of 154 references. There are indexes of subjects and authors.

NONCLINICAL NOTES

ACADEMY OF PSYCHOSOMATIC MEDICINE

At the meeting of the Academy of Psychosomatic Medicine in New York, the following officers were elected: president, Dr. Alfred J. Cantor; president-elect, Dr. Samuel Poindexter; first vice-president, Dr. Harry Phillips; second vice-president, Dr. Carlos Seguin; secretary, Dr. Ethan Allan Brown; treasurer, Dr. George Sutherland; and historian, Dr. Robert Drews.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians, New England States Chapter, elected the following officers for 1955-1956: president, Dr. John B. Andosca, Boston, Massachusetts; vice-president, Dr. Frank G. Seldon, Manchester, New Hampshire; and secretary-treasurer, Dr. Joseph N. Corsello, Providence, Rhode Island.

NOTICES

THE NEW ENGLAND ROENTGEN RAY SOCIETY

The monthly meeting of the New England Roentgen Ray Society will be held at the Hotel Ambassador, Cambridge, Massachusetts, on Friday, November 18.

PROGRAM

4:30 p.m. Film-reading session.
6:00 p.m. Dinner.
8:00 p.m. Manifestations of Acute Abdominal Disease Revealed by Roentgen-Ray Examination. Dr. Barton R. Young, of Philadelphia.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians announces that its fourth International Congress on Diseases of the Chest will be held in Cologne, Germany, August 19 through 23, 1956. The Congress will be sponsored by the Council on International Affairs of the College.

All physicians and surgeons throughout the world are invited.

Further information may be obtained from the executive offices of the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

NEW YORK UNIVERSITY—BELLEVUE MEDICAL CENTER

A meeting of the Animal Care Panel of the New York University–Bellevue Medical Center will be held at the Henry Hudson Hotel, 353 West 57th Street, New York City, on December 1 and 2.

NATIONAL RESEARCH COUNCIL GRANTS

The Division of Medical Sciences, National Academy of Sciences, National Research Council, is accepting applications for grants-in-aid of research in three fields as follows: research in the physiologic, biochemical and pharmacologic effects of alcohol (applications should be received before January 15, 1956); research on the mechanisms controlling sexual behavior in animals and man, involving endocrinologic, neurologic, psychologic, anthropologic, phylogenetic and genetic studies and the physiology of reproduction and related biologic and biochemical fields (applications should be received before February 1, 1956); and research in the fields of analgesia and addiction and information on basic research being conducted in these fields in order to act as a center for the exchange of information, supported by the Committee on Drug Addiction and Narcotics.

Further information and application blanks may be obtained from the Division of Medical Sciences, National Academy of Sciences, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 14. New England Cardiovascular Society. Page 793, issue of November 3.
NOVEMBER 14 and 18. American Public Health Association. Page 578, issue of September 29.
NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.
NOVEMBER 14–30. Consultation Clinics for Crippled Children in Massachusetts. Page 744, issue of October 27.
NOVEMBER 15. South End Medical Club. Page 793, issue of November 3.
NOVEMBER 15, 22 and 29 and DECEMBER 6, 13 and 20. Boston City Hospital House Officers' Association. Page 793, issue of November 3.
NOVEMBER 16, 1955–MAY 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.
NOVEMBER 17 and DECEMBER 15. Arthritis Study Unit. Page 668, issue of October 13.

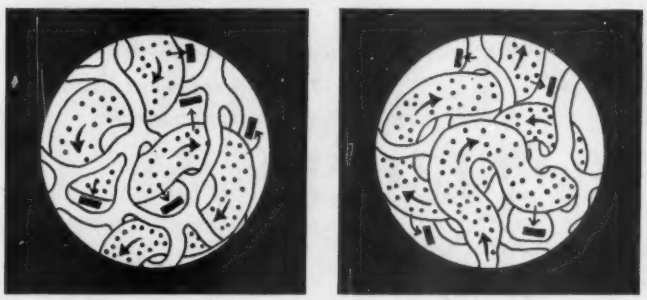
(Continued on page xx)

MICTINE*—THE NEW ORAL DIURETIC

Searle MICTINE Provides Effective Oral, Non-Mercurial Diuresis

The result of many years of research, Mictine, brand of aminometramide, supplies a long-felt need for an improved oral diuretic. Mictine, 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione, is not a mercurial, xanthine or sulfonamide.

Effectiveness: Every method for measuring the diuretic effect in man now available, including precise human bioassay studies, without exception demonstrated that Mictine is an effective oral diuretic, and these studies show that approximately 70 per cent of *unselected* edematous patients treated with Mictine by mouth respond with a satisfactory diuresis.



Mictine is believed to act by the selective inhibition of the reabsorption of sodium ions. Thus, the resulting diuresis is characterized by increased quantities of sodium ions and water.

Well-Tolerated: There are no known contraindications to Mictine, even in the presence of hepatic or renal damage, and there is no risk of acidosis. On high dosage, Mictine causes some side effects in some patients but on three tablets daily these side effects (anorexia and nausea, rarely vomiting, diarrhea or headache) are minimal or absent.

Indications: Mictine is useful primarily in the *maintenance* of an edema-free state and in the *initial and continuing* control of patients in mild congestive failure. Mictine may be used also for *initial and continuing* diuresis in *more severe* congestive states, particularly when mercurial diuretics are contraindicated.

Administration: The usual dosage for the average patient is one to four tablets daily with meals, in divided doses on an interrupted schedule. An interrupted dosage schedule may be accomplished by giving the drug on alternate days or for three consecutive days and then omitting it for four days.

For severe congestive states the dosage is four to six tablets daily with meals, in divided doses on interrupted schedules similar to those already mentioned.

Supplied: Uncoated tablets of 200 mg.

**Trademark of G. D. Searle & Co.*

SEARLE

(Continued from page 840)

NOVEMBER 18. The New England Roentgen Ray Society. Notice above.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 21 and DECEMBER 5, 1955, and JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

NOVEMBER 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.

NOVEMBER 29–DECEMBER 2. American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.

NOVEMBER 30, 1955, and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

DECEMBER 5, 1955, and JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

DECEMBER 5–14, 1955, and JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

DECEMBER 7, 1955, and JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

DECEMBER 9 and 10. Association for Research in Nervous and Mental Disease. Page 745, issue of October 27.

DECEMBER 14, 1955, and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 203, issue of August 4.

JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.

MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.

AUGUST 19–23, 1956. American College of Chest Physicians. Page 840.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 17

THURSDAY, NOVEMBER 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*11:15 a.m.–12:00 m. Thoracic Conference. The Use of Diamox in Pulmonary Emphysema. Dr. Robert E. Quinn. Amphitheater, Peter Bent Brigham Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

*8:30 p.m. Fried Lecture Series. Physiologic Considerations in Origin and Treatment of Neoplasms. Dr. Jacob Furth. Usen Auditorium, Newton-Wellesley Hospital, Wellesley.

FRIDAY, NOVEMBER 18

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

*7:30–9:30 p.m. Postgraduate Medical Institute. Hypertension and Urologic Disorders. Drs. Bartels and Sheddan. Holyoke Soldiers Home, Holyoke.

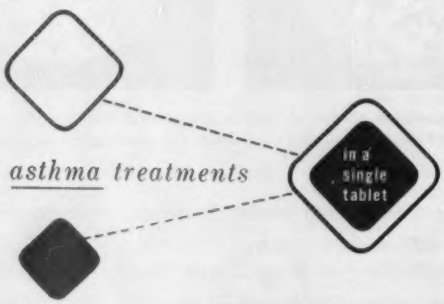
SATURDAY, NOVEMBER 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.

(Concluded on page xxxvii)



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SUPPOSITORY

Ergotamine tartrate	*2 mg.*
Caffeine	*100 mg.*
Bellafoline	*0.25 mg.*
Pentobarbital Sod.	*60 mg.*

Average Dose: 1 suppository at onset of attack; second after 1 hr., if necessary.

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Even her doctors pamper her!

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Each week, doctors from the local Medical Milk Commissions test samples of Cherry Hill Certified Milk. Our own laboratories make tests daily. To further assure the purity of the milk, every Cherry Hill employee must have a thorough once-a-week medical exam.

Hood Cherry Hill is one of less than 50 farms in the nation qualified to produce Certified Milk. We also operate this farm to develop new dairying improvements . . . new methods which are then applied to the *whole* Hood line to constantly give New England better dairy products for better health. This continual striving for perfection is one more reason why — whether it's milk, cheese or ice cream . . . you can recommend Hood with confidence.

	PROTEIN %	FAT %	CARBOHYDRATES %	MINERALS %	CALORIES PER OZ.	CALORIES IN ONE CUP
Hood Certified Milk (whole)	3.39	4.00	4.58	0.72	20.41	163.3
Hood Certified Milk (nonfat)	3.72	0.01	4.98	0.80	11.11	88.9

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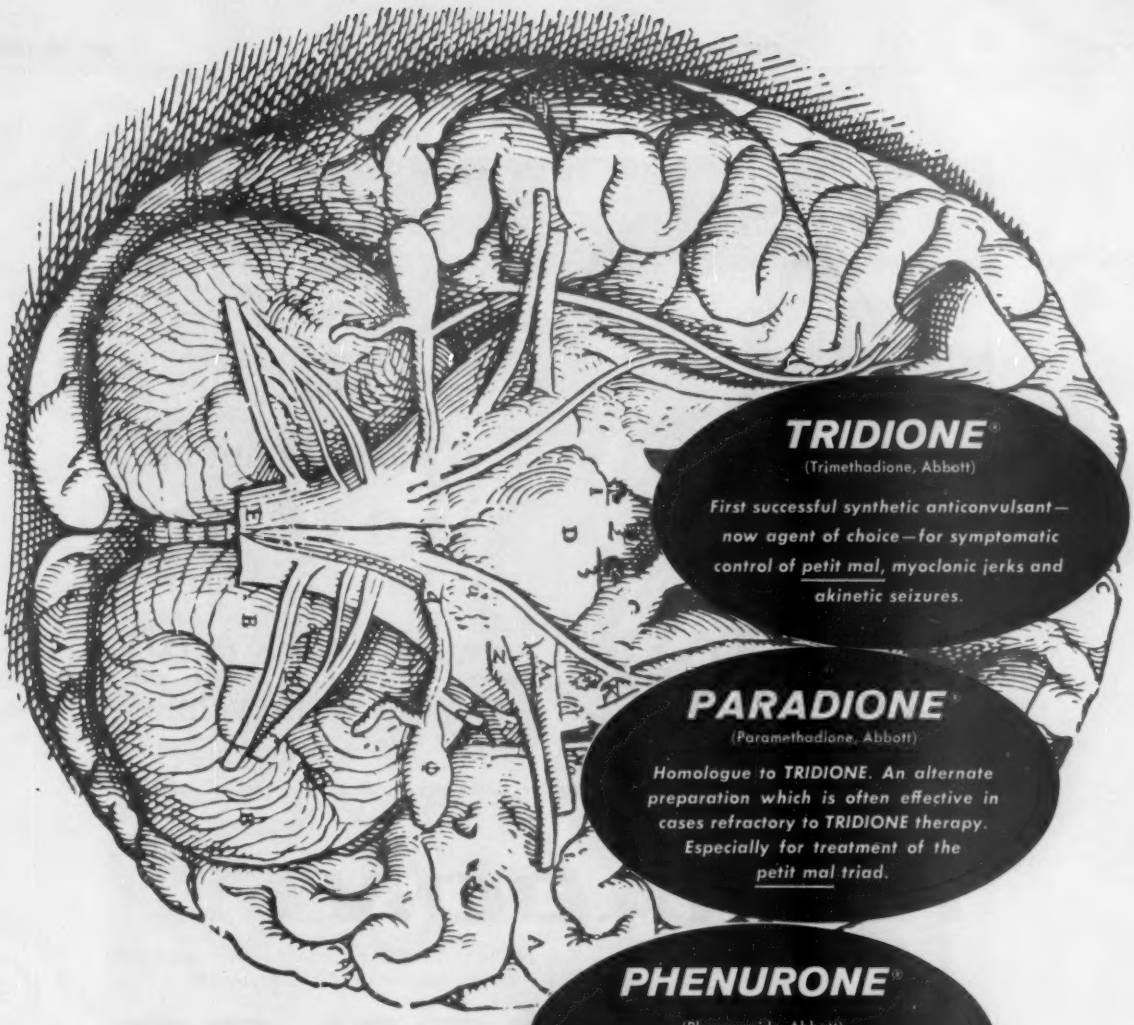

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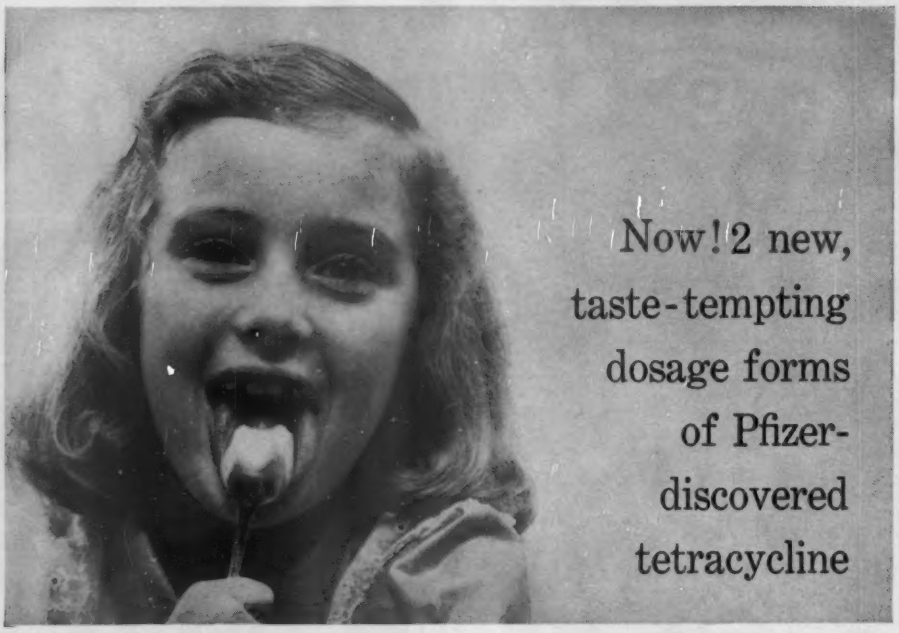

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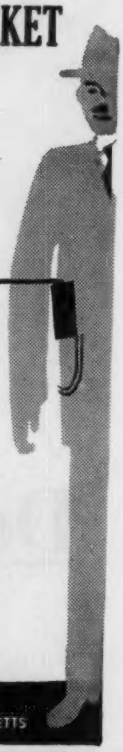

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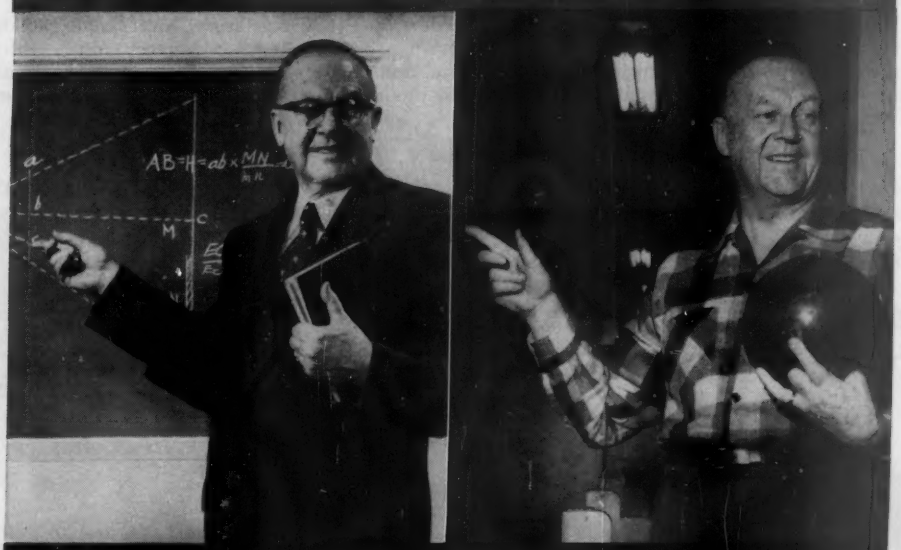

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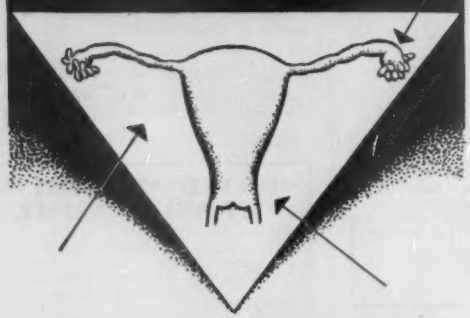

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Jacon Industries	xxx
Kinney & Company, Inc.	iv
Lederle Laboratories	xv, xxvii
Thos. Leeming & Co., Inc.	xx, xxxvii
Eli Lilly and Company	xviii
Medical Clearing Bureau, Inc.	xxx
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Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.)	v, vii, ix, xxiv
Ring Sanatorium	xxxv
Wm. H. Rorer, Inc.	x
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Storrow House (Massachusetts General Hospital)	xxxv
Tweed's Limited	xxxii
United States Brewers Foundation	vi
The Upjohn Company	xxix
Warner-Chilcott	xii
Washingtonian Hospital	xxx
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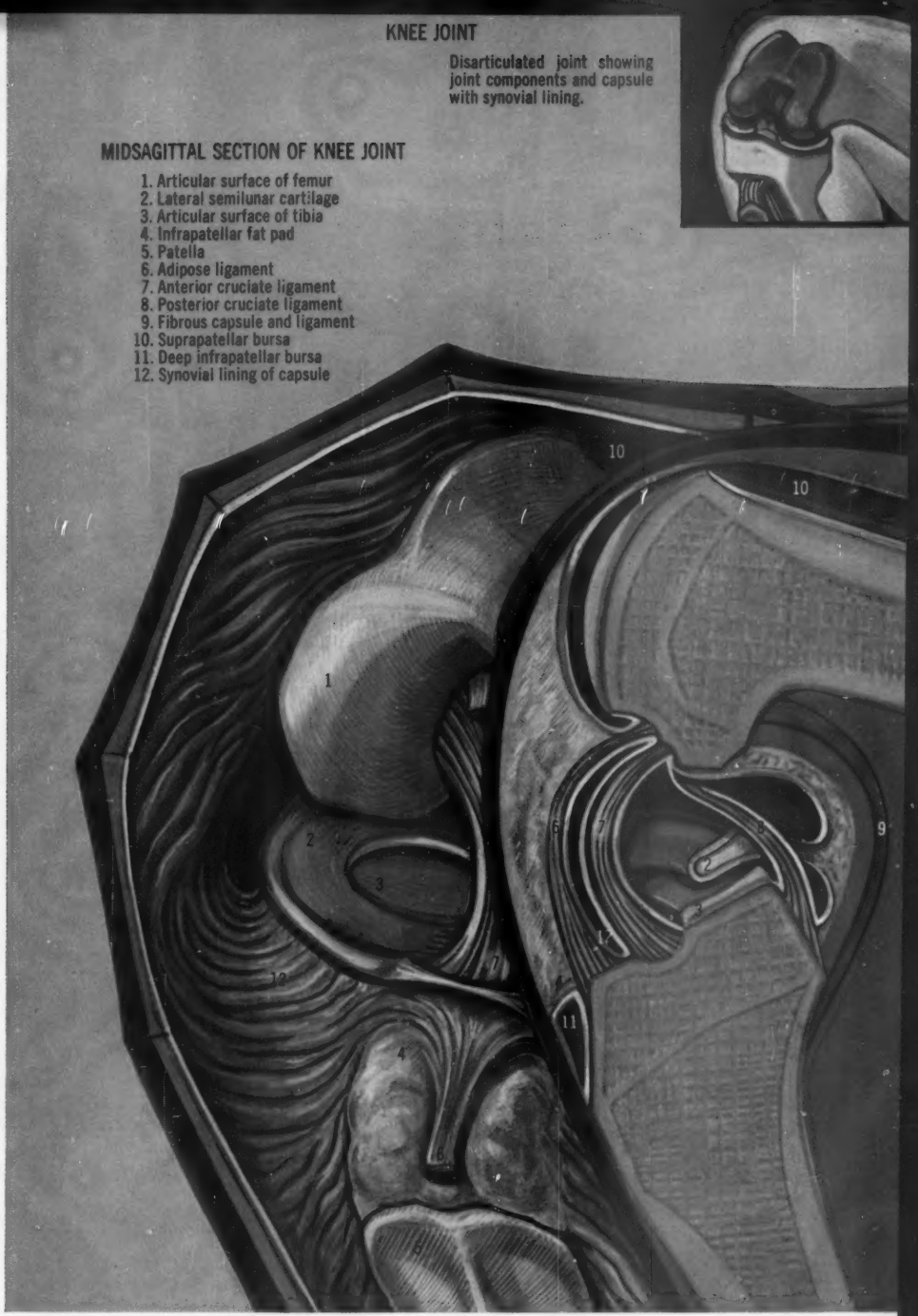
KNEE JOINT
Disarticulated joint showing joint components and capsule with synovial lining.
MIDSAGITTAL SECTION OF KNEE JOINT
1. Articular surface of femur
2. Lateral semilunar cartilage
3. Articular surface of tibia
4. Infrapatellar fat pad
5. Patella
6. Adipose ligament
7. Anterior cruciate ligament
8. Posterior cruciate ligament
9. Fibrous capsule and ligament
10. Suprapatellar bursa
11. Deep infrapatellar bursa
12. Synovial lining of capsule

This schematic representation of a midsagittal section of the knee joint is reproduced from Rheumatology Reviews, No. 7, "The Normal Joint," a publication of the Medical Department of Geigy Pharmaceuticals. This brochure, and others in the same series, are available upo request.

the knee joint

A ginglymus or hinge joint, the knee is one of the diarthroses, which, in general, are among the articulations most liable to undergo arthritic change. Its synovial membrane — the most extensive in the body — covers the inner surface of the capsule and all intra-articular surfaces not covered by cartilage.

Geigy

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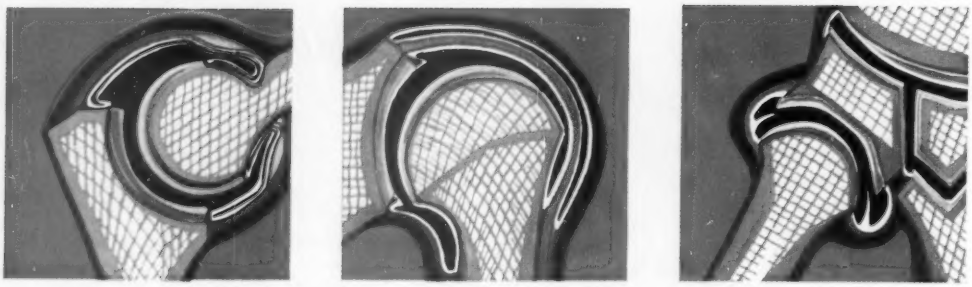

The efficacy of BUTAZOLIDIN in rheumatoid arthritis is clearly substantiated by an analysis of published reports undertaken by Bunim and associates[1] at the National Institute of Arthritis and Metabolic Diseases.

BUTAZOLIDIN being a potent agent, patients should be carefully selected for treatment and dosage promptly adjusted to minimal individual requirements. Physicians should examine patients regularly during treatment and discontinue the drug should side reactions develop. Brochure available on request.

Percentage Response of Patients with Rheumatoid Arthritis*

	BUTAZOLIDIN	CORTISONE	CORTICOTROPIN
Grade I (remission)	6.3	6.7	10.9
Grade II (major improvement)	51.3 → 57.6	32.8 → 39.5	37.5 → 48.4
Grade III (minor improvement)	28.2	37.3	32.8
Grade IV (no improvement)	14.1	23.1	18.8

*Table adapted from Bunim et al.[1]

From this tabulation it may be seen that a total of 57.6 per cent of patients treated with BUTAZOLIDIN show either remission or considerable improvement compared with 39.5 per cent for cortisone and 48.4 per cent for corticotropin.

1. Bunim, J. J.; Sokoloff, L.; Williams, R. R., and Black, R. L.: J. Chron. Dis. *1*:168, 1955.

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57155

(Continued from page xx)

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, NOVEMBER 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Mortality and Morbidity. Dr. Orr. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, NOVEMBER 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. The Role of Surgery in the Treatment of Cancer. Dr. George Crile, Jr. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, NOVEMBER 23

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*11:00 a.m.–1:00 p.m. Postgraduate Medical Institute. Recurrent Abdominal Pain in Children. Drs. Hubbell, Jr., and Welch. Lowell General Hospital, Lowell.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*2:00–4:00 p.m. Postgraduate Medical Institute. Evaluation and Management of Peripheral Vascular Disease. Drs. Crane, Hurwitz, Linton, McKittrick and Robertson. Lemuel Shattuck Hospital, Jamaica Plain.
*2:00–4:00 p.m. Postgraduate Medical Institute. Acute, Recurrent, and Chronic Effusions into the Pleural Cavity. Drs. Lynch and Welch. Norfolk County Hospital, Braintree.
*2:00–4:00 p.m. Postgraduate Medical Institute. Headache. Drs. Hunter and Perlo. St. Luke's Hospital, New Bedford.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*4:00–6:00 p.m. Postgraduate Medical Institute. Systemic Manifestations of Allergy. Drs. McCombs and Patterson. St. Luke's Hospital, Pittsfield.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

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